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Science and Cancer

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A medical scientist explains the nature of neoplastic disease and the efforts of science and medicine to control it.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Science and Cancer

By

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National Cancer Program

The National Cancer Institute of the National Institutes of Health has played a major role in U.S. cancer research since the Institute was founded in 1937.

An expanded National Cancer Program began with the passage of the National Cancer Act of 1971. To carry out the terms of this act, and with funds appropriated annually by the Congress, the National Cancer Institute conducts research and provides grant and contract support for cancer research in most of the Nation's university medical centers and many other non-Federal institutions. The Institute also coordinates the cancer research programs of Federal and private institutions in accordance with a periodically updated national cancer plan, which encompasses the lines of research effort considered to be most important in solving the major problems of cancer. Through the cancer control program authorized by the National Cancer Act of 1971, the Institute ensures the widespread application of research results.

Those who are at the forefront of the struggle to overcome cancer hope and count on the continuing commitment of every American to achieve our common goal—the prevention and cure of cancer.

Director
National Cancer Institute

Preface

Science is advancing against cancer; advancing slowly, but advancing. In this advance, the National Cancer Acts written into laws of the United States in 1937 and in 1971, and the efforts of the American Cancer Society, will loom large on the pages of history.

Public confidence in cancer research remains high, despite all difficulties and the slow rate of progress. There is also scientific confidence that methods of preventing and curing cancer will be found. Current information and reports of progress between investigators and to the public are necessary components in such confidence.

"Science and Cancer" is one such report to the public. Since 1964 some 200,000 copies of "Science and Cancer" have been distributed and it has been translated into Japanese.

In this, the fourth version of "Science and Cancer," the aim remains to synthesize for the general reader the salient facts about cancer. The format and the length remain approximately the same, with alterations being kept at a minimum compatible with currency.

M.B.S.
La Jolla, 1978.

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Contents

		Page
Chapter 1	Introduction: what is cancer?	1
Chapter 2	The dimensions of the problem: cancer in man and animals.	5
Chapter 3	How cancer is diagnosed: the index of suspicion and cellular pathology.	13
Chapter 4	How cancer is treated: surgery, radiation, and drugs.	17
Chapter 5	The outcome of cancer: end results and clinical trials.	23
Chapter 6	Weapons against cancer: men, material, and the scientific method.	29
Chapter 7	Environmental hazards: chemicals that produce cancer.	35
Chapter 8	Radiant energy: sunlight and atomic bombs.	43
Chapter 9	The air we breathe: carcinogens in our atmospheric environment.	47
Chapter 10	Biological carcinogens: viruses that produce cancer.	51
Chapter 11	"In the beginning . . ." A diversion into the meaning of "cause."	57
Chapter 12	Cells and organisms: a complex community.	61
Chapter 13	Within the cell: the new biological frontier.	65
Chapter 14	The crab emerges: the birth and the behavior of cancer.	69

Chapter 15	**Heredity: the biological hub.**	75
Chapter 16	**Hormones: internal regulators of growth.**	79
Chapter 17	**The food we eat: nutrition and cancer.**	83
Chapter 18	**Immunity: trained guardians against invasion.**	87
Chapter 19	**Chemotherapy: a frontal attack.**	93
Chapter 20	**The past and the future: victory is a reasonable expectation.**	99
Bibliography		103
Glossary		105

1. Introduction

What is cancer?

Cancer is now the most feared of human diseases. Its victims are counted among men and women, among children as well as the aged, among all races, among all walks of life—athletes, actors, political leaders, and the common people throughout the world.

There are few families in the United States who have not had personal experiences with cancer. This is almost inevitable, because now cancer is the number two scourge of our people, destined during the whole of our lifetime, of over 70 years, to afflict one of each four of us, and to send one of each seven of us to the grave. Every 2 minutes someone in the United States dies of cancer. Every year the direct cost of cancer is in the billions of dollars, cold figures that do not measure human suffering by the victims and grief to their families. Yet this is a measure and the price of our victories over some of the original horsemen of Apocalypse. For most of the fortunate citizens of the United States, the pale rider of pestilence is now retired, and the cadaverous rider of hunger is too obese to maintain his seat. We now face different riders, one in the shape of a mushroom cloud, and one in the shape of a crab.

Great credit is due to the intelligence of the American people for removing many of the taboos and secrecies that surrounded cancer just a few decades ago. We now accept openly and write freely that human beings have rectums and vaginas, and that diseases of any cause and any part of our body require public knowledge. We are now better informed and resultantly stronger. Secrecy and ignorance lead to fear. And, as Shakespeare said, fear is more pain than is the pain it fears.

The other side of the picture of better public information is the complexity and the unending volume of technical reports that are often presented without adequate background. Issues of scientific journals, announcements from scientific institutions, meetings of scientific societies produce a torrent of reports that are boiled down for use by newspapers, and carried throughout the world by the news services. New cancer tests, new causes of cancer, new drugs that are claimed to have produced remissions of cancer are thus presented to the public eye. The stories are soon forgotten, because too many are overinterpreted or out of context. Science seldom advances by great leaps, or by massive breakthroughs that are announced at meetings. Its processes are usually much slower, through the accumulation of information and verification by many workers, until a definite step of progress becomes evident to all. By then the step may be considered no longer newsworthy by journalistic standards. This happens so often that one facetious physician once divided accounts of scientific discoveries into two classes: the dramatic, unimportant ones, and the undramatic, important ones.

One reason why this is true is that it takes time to establish the proper place of many observations within the framework of science and medicine. A new treatment for cancer is described. If this treatment were truly useful, the author must be able to present what has happened to his patients several years later. If he does not have such information, he must wait for the necessary years to elapse.

But the patient who has cancer *now*, and the physician who must decide how to treat that patient *now*, cannot wait several years for the conclusion. For the decisions that have to be made now for ourselves and for those who depend on us, we must separate carefully the best information that is available from the hopeful trends that may lead us to better answers in the future.

What can we do, and what should we do, about cancer? And what are the research scientists finding and developing in the laboratories and clinics? These are the two questions with which this report is concerned, and which it attempts to answer in the light of our current knowledge.

But, to start at the beginning, what is cancer?

First of all, cancer is a word in the English language, derived from the Greek word for crab, *karkinos*. Among its many synonyms are malignant tumor and malignant neoplasm (from the Greek for new growth). Subgroups of cancer, describing the body tissues of origin, include carcinoma, sarcoma, melanoma, lymphoma, and many other related or combined terms.

Cancer is a word that stands for a great group of diseases that afflict man and animals. Cancer can arise in any organ or tissue of which the body is composed. Its main characteristics include an abnormal, seemingly unrestricted growth of body cells, with the resultant mass compressing, invading and destroying contiguous normal tissues. Cancer cells then break off or leave the original mass and are carried by the blood or lymph to distant sites of the body. There they set up secondary colonies, or metastases, further invading and destroying the organs that are involved.

This semi-independent behavior of cancer cells, in contrast to the disciplined behavior of normal cells that allows them to fulfill functions useful to the body, is called *autonomy*.

Another important characteristic of cancer is its appearance under the microscope. The individual cells vary in size and shape, and the orderly orientation of normal cells is replaced by disorganization that may be so complete that no recognizable structures remain. This loss of normal appearance is called *anaplasia*.

At the present time, cancers are classified by their appearance under the microscope, and by the site of the body from which they arise. By such criteria of appearance (morphology) and localization, devised by pathologists during the past century, at least 100 different cancers are identified. The number can be increased to 200 or more if finer details of morphology are taken into consideration.

There are, of course, other differences between cancer entities. Some cancers grow very slowly, and destroy neighboring tissue by local invasion. Others are very aggressive and disseminate rapidly to distant sites. Most cancers occur with increasing frequency among older people, but some forms of cancer are found most often in children. About some cancer entities we know much and can prevent their occurrence. About many cancers, our knowledge regarding cause is still entirely lacking.

Thus, cancer is a group word that encompasses many different entities that are dissimilar in appearance, in behavior, and undoubtedly in the causative factors as well. Cancer as a word therefore shares in the difficulty common to all group words: it is a convenient general term that must be used carefully when we are dealing with specific situations. In an intelligent discussion of cancer as a clinical problem of an individual patient, or as a research topic of an experimental animal tumor, we must identify the specific type of cancer and the specific conditions of the situation. These specific conditions should not be extended to other cancer entities, or to the whole group of cancers, if confusion and misunderstanding are to be avoided. Many of the seeming paradoxes regarding cancer can be attributed to the extension of the specific to the general, on the one hand, and the application of the general to the specific on the other hand.

For convenience, we have discussed cancer and normal cells as two sharply separate, different entities. Actually, there is a wide spectrum of cellular abnormalities and normal reactions between these extremes. The rate of cell division and tissue growth of a normal pregnancy exceeds the rate of growth of many cancers, with the key difference being that the normal process stops when it has reached its end point. In appearance also, the normal repair of injured tissue may for a time look quite "wild" under the microscope, but represents a self-limiting reaction. There is also a spectrum between the benign, or innocent, tumors, and cancers, including a zone of borderline lesions regarding which decision is particularly difficult. As a further complication, a tumor that may seem benign in microscopic appearance can be fatal if located in a vital area or in a limited space, such as the brain.

2. The dimensions of the problem

Cancer in man and animals

The diseases grouped under cancer are second only to another group of diseases, of the heart and blood vessels, as killers of the people of the United States. This is also true of European and other countries that have kept pace with modern public health technology, and have reduced tuberculosis, other infectious diseases and malnutrition to relatively unimportant roles.

In numbers, among the 218 million people in the United States in 1978, approximately 700,000 develop cancer during 1 year, and approximately 390,000 die of cancer during 1 year. It is more convenient to express these facts in ratios, using 100,000 people as a standard number and a year as a standard time period. We would then say that the annual crude incidence and mortality rates of cancer are 321 and 179 per 100,000 respectively.

We should note that these are "crude" rates. By this is meant that they have not been adjusted for the age distribution of the

population, which is of great importance in considering diseases that occur in higher frequency among older members of the population. There has been a steady, striking rise in the number of cancer deaths in the United States during the past 50 years. Some of this rise is undoubtedly due to better diagnosis of cancer, and better reporting of cancer cases. But a much more important factor has been the increasingly older population, saved from earlier death from other causes. If this aging is taken into consideration, and statistics from different years adjusted to a similar age distribution, the death rate from cancer between 1950 and 1976 increased among men by 24 percent, and decreased among women by 8 percent. Among people under 45 years of age, the cancer death rate dropped from 24.2 to 14.7 per 100,000.

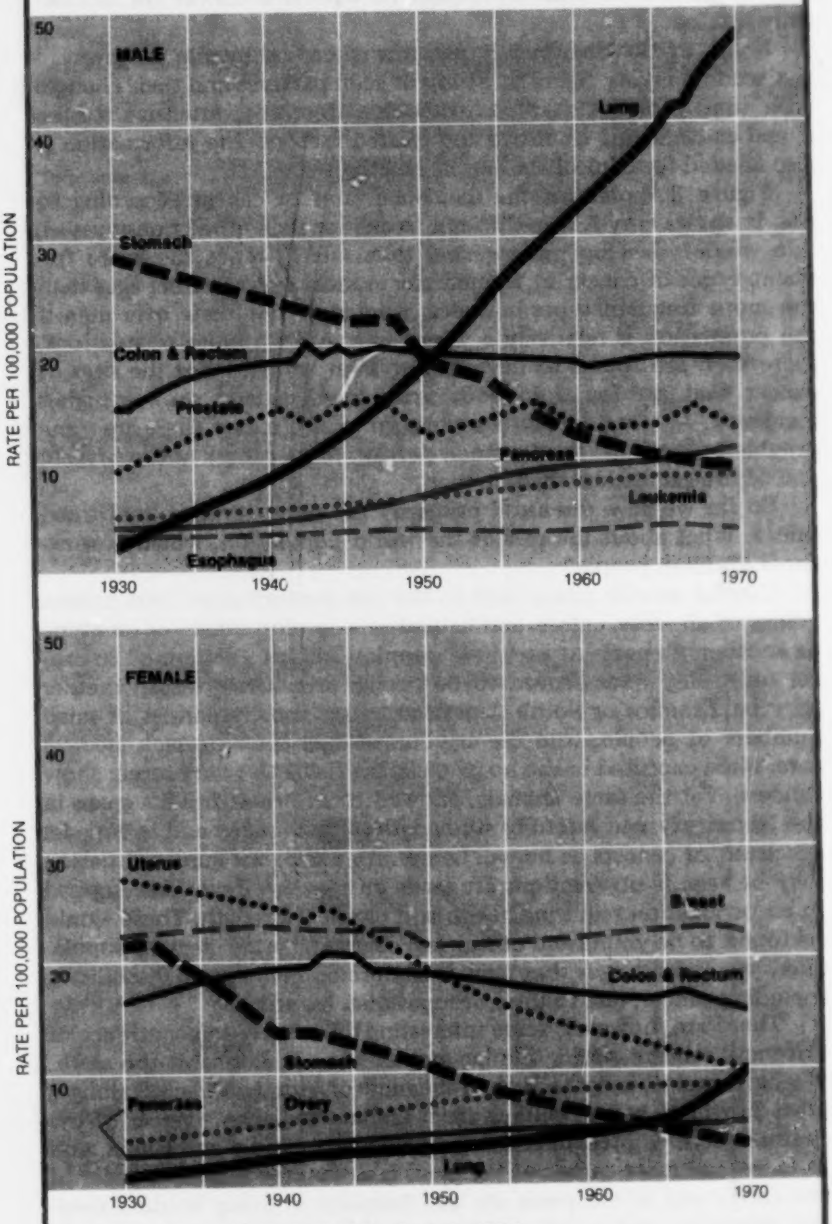
Some remarkable changes have occurred in certain types of cancer, as indicated in figure 1, and these changes provide us with clues regarding causation that may lead us to eventual control over these diseases. The most striking change has been observed in the increase of lung cancer. This cancer, relatively rare only 40 years ago, is now the top cancer killer of men and accounts for the recent increase in cancer mortality among women.

As interesting and as important as the rise in lung cancer has been the impressive drop in the death rate from cancer of the stomach. During the past 30 years, in women as well as in men, this cancer entity has dropped in occurrence by about 50 percent. We do not understand the reasons for this happy situation. Cancer of the stomach does seem to be a disease of underprivilege and cold climate, occurring more frequently among the lower socioeconomic classes, and among the people of Iceland, Scandinavia, Russia and Poland, and Japan. Epidemiologic and laboratory studies focused toward a more specific definition of the factors that are involved may provide us with leads for further reduction of this important form of cancer.

In the United States, the last 30 years also have shown a steady increase in the reported deaths from leukemia and related cancers of the blood and lymphatic systems, and a decrease in mortality from cancer of the uterine cervix in women. Part of the latter effect is due to better treatment. The salvage rate of women with cancer of the uterus and cervix is improving continually, particularly as a greater proportion of the cases is detected at earlier stages by the use of the vaginal smear technique introduced in the United States by George N. Papanicolaou of Cornell University Medical College. The Third National Cancer Survey of 1969 revealed a rise of 20 percent in cancer incidence among blacks, with greatest increases in cancer of the pancreas, prostate and esophagus.

In the United States and many European countries, the most common forms of cancer among women are cancers of the breast, the uterus, and the large intestine, with lung rising rapidly. Among men, the lung, prostate and large intestine are among the most fre-

FIGURE 1. TIME TRENDS IN CANCER MORTALITY RATES, BY SITE AND SEX: United States, 1930-1970 (age-adjusted to U.S. 1940 population).



Source: "Cancer Rates and Risks," ed. 2, 1974.

quent sites in the death statistics. In terms of incidence, skin cancer ranks high among fair-skinned males, but this is not apparent in the death registries because most patients with skin cancer are successfully treated.

Some of the distribution patterns of cancer by site are given in the accompanying figure 2. Study of such patterns and their changes with time provides scientists with clues for more intensive studies aimed at clarifying causative and related factors. The information is also needed for clinical and public health uses.

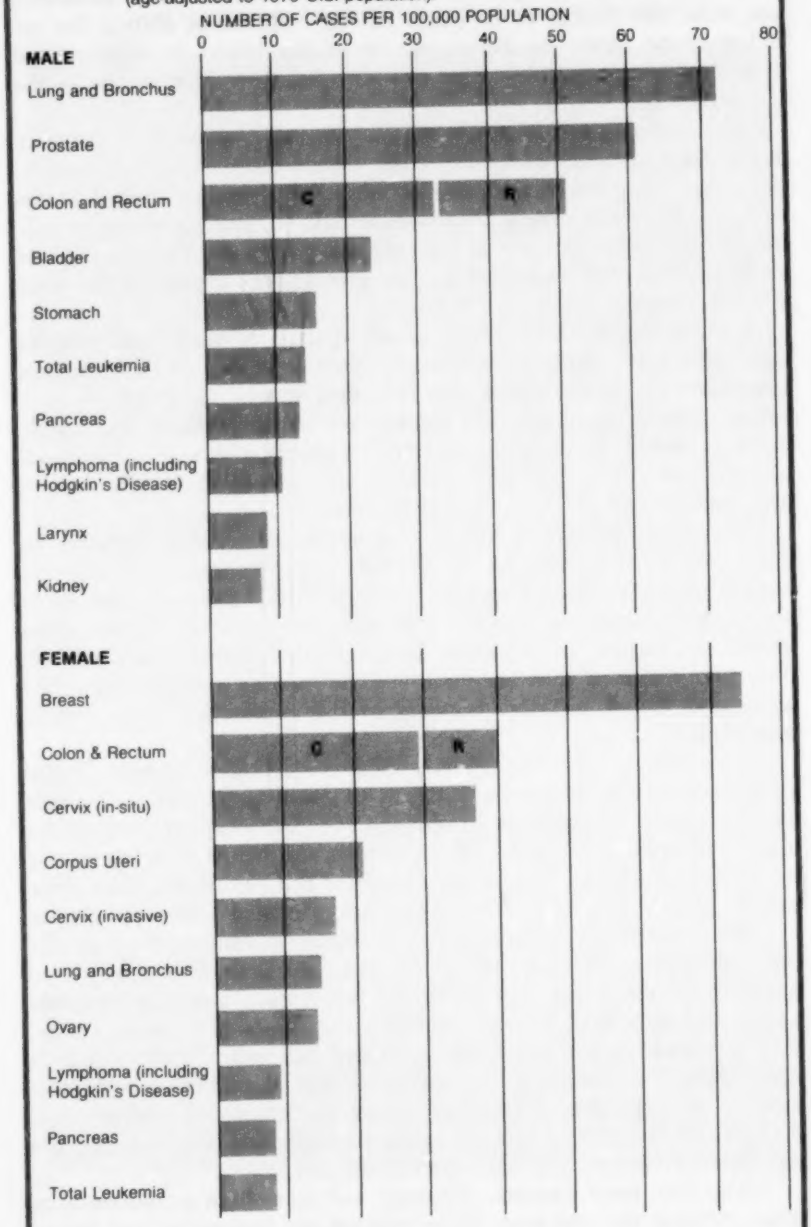
Figure 3 represents the incidence rates of cancer according to age. It shows why it is so difficult to answer such broad questions as, "do women develop more cancer than men?" Since the more frequent types of cancer in women rise in incidence at earlier ages than the more frequent types in males, women predominate over men if the population is relatively a young one. Among older populations, more men are found to have cancer than women. For the sites of cancer that are found in both sexes, men usually show a higher incidence. As usual in this complex group of diseases, there are some notable exceptions: thus, women develop more cancer of the thyroid and of the gallbladder than do men.

So far we have discussed primarily the population of the United States. What about the rest of the world population, which now exceeds 4 billion people?

Careful studies going back to the last century show that human beings of all races, colors, and habitations develop cancer of one type or another. Reports of primitive peoples that are "immune" to cancer uniformly have proved to be wrong. Primative groups, whether they be Eskimos or South American tribes, usually consist of small numbers of people, who die at younger ages and who lack medical care. Mice captured in the home or in the fields also very rarely show cancers. Yet the same animals, allowed to live their full life spans in the laboratory and carefully studied, develop as many and as varied a spectrum of cancers as human beings. An analogous human situation may be seen if observations are made on a group of workers engaged in an occupation requiring health and physical strength. These would be found to be young and having less disease than the general population, yet at later ages they may well develop many more disabilities, including cancer, due to their occupational hazards.

There are, however, some interesting differences in occurrence of different cancers among human populations that inhabit the earth. We have mentioned the high frequency of stomach cancer along a great northern belt extending from Iceland to Japan. Cancer of the uterine cervix is preeminent among women of India and China, and in these countries cancer of the penis is a common disease. Cancer of the cervix and of the penis are also frequent in many South American countries, and in other countries with relatively poor standards of personal hygiene. Cancer of the liver is several times more fre-

FIGURE 2. CANCER INCIDENCE BY SITE AND SEX: United States, 1969-1971 (age-adjusted to 1970 U.S. population).



Source: "Cancer Rates and Risks," ed. 2, 1974.

quent among peoples of the sub-Sahara belt of Africa and in Indonesia than it is in Europe and in the Americas. Cancer of the skin is less than one-fourth as frequent among Negroes as among the so-called white races. In Japan, cancer of the breast in women, and cancer of the prostate in men are one-fourth as frequent as in the United States.

Studies of populations that have migrated show that the incidence rates of many cancers change toward those of the new habitation. As examples, Scandinavians now living in the United States have less stomach cancer than in Scandinavia, and Japanese in California have more colorectal cancer than in Japan. These shifts are attributed to environmental factors and suggest directions for their identification.

Cancer has been observed in all species of vertebrate animals that have been studied adequately, meaning that careful autopsy examinations were carried out on, say, several hundred of such animals reaching old age for their species. In fact, cellular abnormalities that resemble cancer are observed in plants, such as the crown-gall of tomatoes. Cell masses that resemble cancers of higher animals have been studied and produced also in insects.

Fish develop cancers identical in appearance and in behavior to those seen in man. Among the amphibians, the common frog, *Rana pipiens*, develops kidney cancer, which is attributed to a virus. Birds have a wide variety of cancers, and one of the most important is the leukemia complex of chickens. In the United States, practically all flocks are infected with the virus entities causing not only leukemia of several types, but also cancers of the connective tissue, called sarcomas.

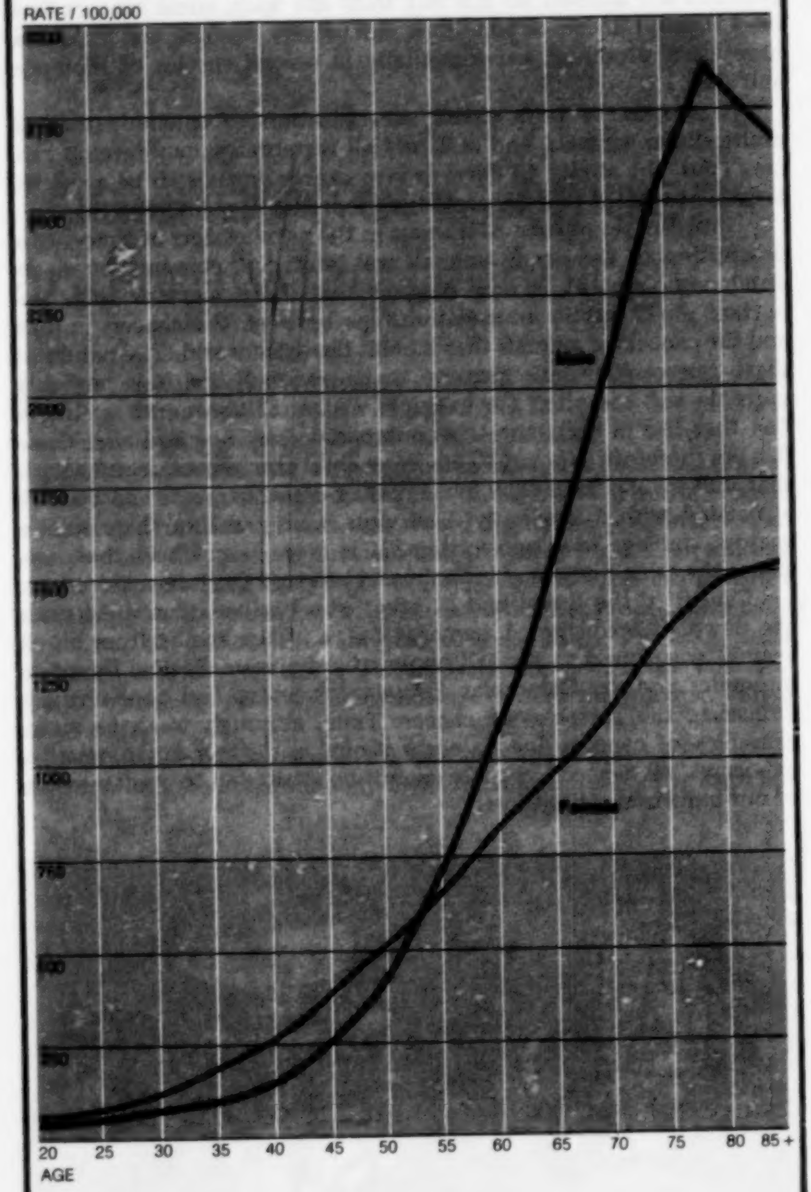
A variant of leukemia, usually localized to lymph glands, is also an important disease among cattle. The white-faced Hereford cattle develop cancer of the skin around the eye following exposure to the intense ultraviolet radiation of our deserts and plains. It is interesting that cows practically never have cancer of the breast. Among horses, cancer of the skin and of the penis are the more common forms.

The favorite pet animal of the American people is the dog, and there are extensive observations on very old dogs. They show that dogs are prone to develop cancer of the breast, testis and adrenal gland, and leukemia. In some localities of the southeastern United States, dogs have cancer of the esophagus following infestation by a small worm that lodges in the surrounding tissue. There is a venereal sarcoma in dogs that is transmitted by sexual or oral contact, and that has an interesting characteristic of regressing and healing in a significant proportion of the afflicted animals.

Cats, too, have cancers, although not in as high a frequency as dogs. Among the common feline tumors are leukemias and breast cancers.

Only a few species of monkeys and anthropoid apes have been

FIGURE 3. AGE-SPECIFIC CANCER INCIDENCE RATES BY SEX: United States, all races combined, all sites (except skin and carcinoma-in-situ), 1969-1971.



Source: "Cancer Rates and Risks," ed. 2, 1974.

studied adequately, but it does seem that the common rhesus monkey develops relatively few cancers. Nevertheless, when these primates are allowed to live out their life span, some cancers have been found. Cancers of bone, liver and urinary bladder, and leukemia, have been produced experimentally in several species of monkeys and apes.

It appears to be a sound generalization to conclude that all multicellular animals, and certainly all vertebrates, can develop cancer. Thus, the ability to develop into cancer appears to be a characteristic of all cells that are capable of reproduction and growth.

Until the resurgence of interest in the virus aspects of cancer, the description of cancers in animals was limited to comparative, anecdotal pathology. It is now obvious that there must be some important albeit subtle interrelationships between the cancers in man and the cancers in animals that inhabit the same world. The nature of these interrelationships remains to be clarified, and it is probably multiple and complex. For example, cancer of the mouth occurs in fish that live in harbor waters contaminated by tars and oils. These fish are therefore exposed to environmental cancer-producing hazards that also involve man. The leukemias of chickens, mice and cats are associated with a similar type of virus, and probably share similar vectors, carriers and transmitters. It is more than likely that man shares the same hazards as his animal relatives.

Cancer of the breast and of other sites has been described since the dawn of medicine. A hemangioma, a tumor arising from blood vessels, was found in the tail bones of a dinosaur. Several Egyptian mummies and pre-Columbian Peruvian skeletons had bone changes indicating the presence of cancer. Thus, although we have many examples of cancers due to occupational and other environmental exposures, all cancers certainly cannot be attributed to contaminants of our industrial civilization.

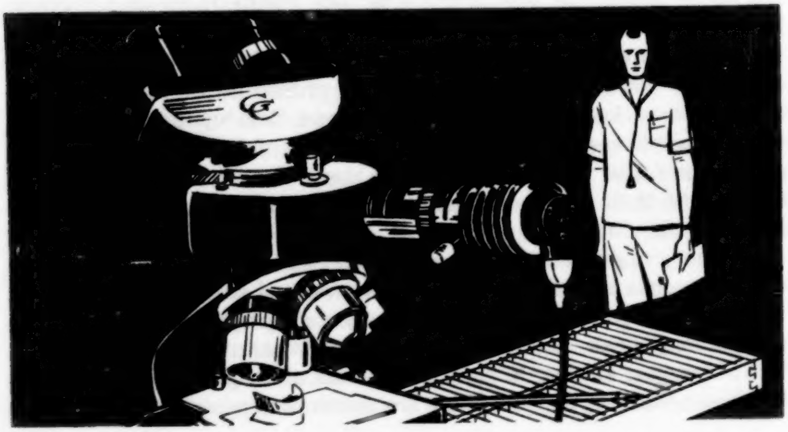
3. How cancer is diagnosed

The index of suspicion and cellular pathology

In the foregoing chapter we have sketched some facts about cancer as it affects populations. In this and the following two chapters we shall deal with cancer as it affects individuals.

We have stressed the diversity of entities that comprise cancer. This diversity probably precludes the discovery of a single reliable laboratory procedure or test that would diagnose all cancers. We can say certainly that there is no such test known at present. Depending on the suspected site or type of cancer, as based upon the patient's complaints or the physician's suspicions, a different set of diagnostic procedures is undertaken. The last of these steps, the basis upon which all diagnosis of cancer is acceptably founded, is the examination of a relevant piece of diseased tissue under a microscope. This is called a *biopsy*.

For cancers of the internal organs, the steps between initial suspicion and definite diagnosis may be many and complex. The steps are



targeted at three questions a physician must answer in considering a patient's problems. These questions are: what is it? (diagnosis); what should be done? (therapy); what is the probable outcome? (prognosis). Cancer is always a medical challenge because the life of the patient depends upon the earliest diagnosis and the correct first treatment.

The most curable cancers are cancers that have not progressed to the stage of producing symptoms. Such cancers usually are small and localized. Periodic examinations of individuals without symptoms are well worth while for the detection of many incipient diseases. Periodic examinations should be a primary aim of any comprehensive health and medical care system for a population. The development of multiphasic screening techniques will make this increasingly feasible. No examination will detect *all* cancers, and many procedures that must be employed in the face of symptoms are uneconomical to consider for symptomless individuals. Economy here is not used in monetary sense, but as it relates to the time, discomfort, and hazard to the patient.

Examinations that have stood the test of experience as being worthwhile in the detection of symptomless cancer include a general physical inspection and palpation of the whole body, with special attention to the cavities of the mouth, the vagina, the bladder and the rectum. The vaginal smear test for cervical cancer should be a routine annual procedure on all women of adult age. If this test were performed on all women, the mortality from this important cancer site could be reduced by about 90 percent. The examination of the rectum by means of lighted tubes, called proctosigmoidoscopy, is unquestionably useful in detecting this common form of cancer at stages that are curable by surgery. Soft-tissue X-rays of the breast, or mamography, should be part of the periodic examination of all women over 50.

Every individual should know and be aware of his or her body. Periodic self-examinations are an excellent health practice. Women should examine their breasts once a month, for lumps, thickenings and other abnormalities. A systematic procedure of inspection before a mirror, and gentle palpation has been developed by the American Cancer Society. Periodic examinations of the skin, mouth and genitals are also useful. Men should know the normal size and consistency of their testes, and check them for enlargement, hardness or irregular contour.

Under conditions as they exist at present, most cancers are diagnosed because an individual becomes aware of certain symptoms, or because a physician suspects that certain symptoms or signs of a patient may mean that a cancer is present. What are these symptoms? The American Cancer Society in its education program emphasizes the Seven Warning Signals. They are worth remembering:

1. Unusual bleeding or discharge
2. A lump or thickening in the breast or elsewhere
3. A sore that does not heal
4. Change in bowel or bladder habits
5. Hoarseness or cough
6. Indigestion or difficulty in swallowing
7. Change in a wart or mole.

If a signal lasts longer than 2 weeks, see your doctor. The actual number of possible symptoms is legion. None of the symptoms, however, means that cancer is necessarily present, because they can be due to many other causes. They are danger signals that require medical attention.

The physician begins a time consuming, systematic detective action that has three main divisions: a careful history, which may allow a patient to recall events that may be of utmost relevance to his situation; a thorough physical examination, including the use of instruments through which the physician can see parts of the intestinal, respiratory and the genital and urinary canals; and laboratory procedures, especially X-rays. Computer-aided tomography (CAT) is a recent development in X-ray equipment that allows better visualization of internal masses. Ultrasound is another recent addition to diagnostic procedures. All these may lead to the identification and localization of a mass or a "lesion" which can be reached only by surgical operation. This is often the case not only for such internal cancers as of the lung, stomach and other organs of the abdominal cavity, but of the breast, muscle or bone. The cancers that are more likely to respond to treatment are those that cannot be distinguished from other diseases before an actual biopsy is obtained. The small piece of tissue that is removed is placed in a preservative, cut in very thin slices, placed on a glass slide, stained with special dyes, and examined under the microscope. The procedure may be done in the operating room, by rapidly freezing the tissue, so that the operation can be continued if the presence of cancer is established.

For specific sites and types of cancer, a wide variety of laboratory procedures are useful in diagnosis and subsequent observations on patients. Some cancers, as part of their biology of abnormal growth, overdo the functions of the tissue from which they are derived. Tumors of the pituitary gland may secrete too much growth hormone so that the patient develops overgrowth of his bones and other evidences of acromegaly. Tumors of the adrenal gland may oversecrete cortisone and related hormones and produce a physical appearance called Cushing's disease. Women may start growing beards and in other ways become masculine with certain rare tumors of the ovary, and excrete grossly increased amounts of sex hormones in the urine. A wide variety of biochemical tests on urine and blood is available for specific situations of differential diagnosis. Many of these tests are useful also in following the course of the disease under treatment.

The cytology test, developed for cancer of the uterine cervix, has been extended usefully to other locations in the body. Detection of abnormal cells in the urine is helpful in the diagnosis of cancer of the urinary bladder. Abnormal cells are looked for also in sputum, smears of the nose and mouth, and in washings of the stomach. Cytologic evidence alone is seldom conclusive, however, and should be followed by an actual biopsy for the definite diagnosis of cancer.

Thus, the diagnosis of cancer is reached by a pathologist looking through a microscope at a small piece of stained tissue. In order to reach the correct answer, two elements are demanded: the tissue on the slide must be taken expertly and from the right spot, and the man looking into the microscope must have the experience and the judgment for the interpretation, on which the outcome of the case must depend. It is immediately obvious that human error is inevitable. For some common forms of cancer this error is almost negligible, especially if the lesion is not in its earliest stages. But for other, rare cancers, such as bone sarcomas, melanomas and lymphomas, the margin of error may be considerable, even on such a basic point as whether it is a malignant tumor at all.

Here often is the explanation of the miraculous cure claimed by a quack. A lesion that is diagnosed as cancer that is not a cancer is curable by any, or no, treatment. Here is also the tragedy of recurrence and wide spread of a disease that was considered to be a benign one. Fortunately, these occurrences are not frequent, and become less frequent as the training and the experience of physicians and pathologists improve. It is also true that difficulties in diagnosis will increase as patients bring smaller and earlier lesions to the attention of physicians, and as the physicians confront the pathologists with progressively earlier stages of cancer.

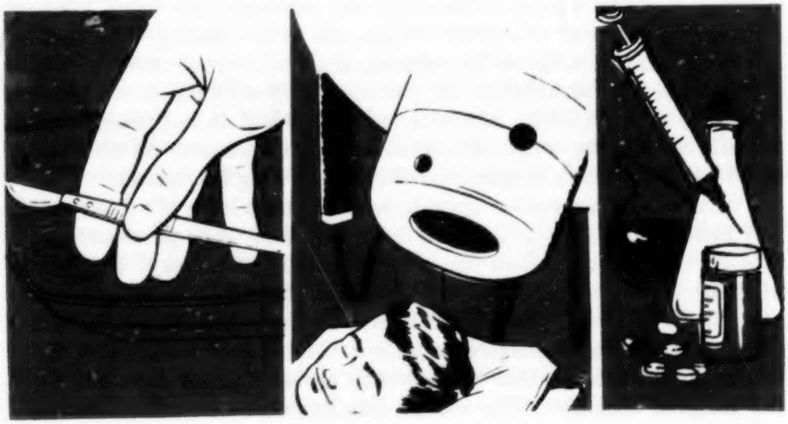
Cancer diagnosis by pathology is based upon correlations between microscopic appearance and clinical outcome. Lesions that resemble cancer but do not progress or spread are reclassified as benign. Lesions that appear benign but recur and metastasize are reclassified as malignant. Such correlations are now being extended to finer details observed under the electron microscope, and to biochemical characteristics of the tissue. In breast cancer, for example, clinical response to hormones is related to the presence of estrogen-receptors in the cancer cells.

4. How cancer is treated

Surgery, radiation, and drugs

The key to successful treatment of cancer is to diagnose it at a stage when the cancer can be removed entirely from the body. We have at our disposal two methods by which such removal can be accomplished: by surgery, or by X-rays. These are not alternative techniques for all forms of cancer. Some forms of cancer are "radioresistant," or not responsive to doses of X-ray that can be given safely to the patient, whereas other forms are sensitive to X-rays and are called radiocurable or radiosensitive.

In the United States, some 80 percent of patients receive initial treatments aimed at curing the disease; 20 percent are too far advanced for such treatment. Surgery is the primary form of treatment in 45 percent, and in another 10 percent surgery is combined with radiation. Radiation is the primary treatment in about 20 percent. Chemotherapy is given to less than 10 percent as the first form of treatment, but is used in a large proportion of patients with recurrences.



Among the radio-resistant cancers, which must be treated by surgery, are the cancers of the gastrointestinal tract and the associated organs, including the stomach, small and large intestines, gallbladder, pancreas and liver. Surgical resection is also the primary curative approach to brain tumors, cancers of the breast, kidney, testis and ovary, and bone and muscle.

Very radiosensitive cancers, such as those arising from the lymph nodes and blood-forming tissues, of which Hodgkins' disease and lymphosarcoma are examples, are best treated by X-rays in combination with chemotherapy. For cancers of the mouth and the face, the uterine cervix and the urinary bladder, either surgery or X-rays may be selected as the primary treatment. Chemotherapy may be used alone in patients with leukemia and other disseminated cancers.

There are, of course, many modifications of techniques used by surgeons and by radiotherapists. The ideal management of most patients with cancer is by a smooth-working team of a surgeon, radiotherapist, pathologist and medical oncologist, with consultations between the specialists not only at the initial decisions regarding treatment, but as the case progresses. In medicine, responsibility over a patient is not safely divided between doctors, and at any given time the primary management of a patient must remain in the hands of one of the clinicians.

Inadequate surgery or radiotherapy, which at the initial course of treatment does not include the total extent of the cancer, is not only doomed to failure but may well spread cancer cells and speed up the fatal course of the patient. That is why even the ancients, whose experience with cancer was usually limited to cancer of the breast, followed the principle of Hippocrates, "primum non nocere," meaning, "first do not harm."

Surgical resections of internal cancers became possible following the discoveries of two great boons to mankind, anesthesia and asepsis, during the 19th century. The German surgeon, Theodor Billroth, remains a giant of the early era, especially for his operations on the stomach and intestines. During the 20th century, with further improvements of surgical techniques, and the introduction of blood transfusions and antibiotics, all portions of the human body became surgically approachable. American surgeons had an important role in the developments, with Harvey Cushing's operations on the brain, and Evarts Graham's surgical removal of the lung for cancer.

Increasingly extensive operations for cancer have been perfected, and cancers of the cervix, head and neck that were previously considered beyond operation are now accepted for surgery. The use of heart-lung pumps, artificial kidneys, and the replacement of bones and blood vessels were forerunners of transplantation of whole organs, and further surgical miracles. Control of shock by blood transfusions, and control of infection by antibiotics have extended the surgical frontiers. The recent development of total intravenous alimentation, by infusions into the main veins of the body, allows better support of debilitated patients. At the same time, experiences with more conservative resections of cancers of the breast, thyroid and other sites show that these more limited procedures also have a definite place in the treatment of cancer. The question is not whether radical or more limited surgery is superior, because both have their place. The planning of cancer therapy focuses instead on selection of the best procedure for the individual patient.

Radiotherapy uses X-rays, radium, and other sources of ionizing radiation for the destruction of cancer. The monumental discovery by Wilhelm Roentgen, in 1895, of the penetrating new electromagnetic rays, led to their use in diagnostic procedures almost at once. X-rays were soon known to have a destructive effect on normal tissues, and by 1910 these effects were shown to lead to the development of cancers. Several clinicians also observed that exposure of skin cancers to X-rays made them disappear, as earlier workers had seen with radium. A systematic study of the place of ionizing radiation in the treatment of cancer became possible. Claude Regaud and Henri Coutard of France were among the influential pioneers who worked out the source, the sequence of doses, and the filtration and distance factors that allowed quantitation of the radiation factors. Higher speeds, deeper penetration, sharper delineation and greater sparing of surrounding tissues have been achieved with the introduction of multimillion volt and radioactive cobalt sources. New types of high-energy subatomic particles, such as neutrons, heavy ions, and pions, are being explored against cancer, in hopes of extending the therapeutic effects. Radiologists, like the surgeons before them, are going through a period of evaluating greater doses and larger fields in a variety of cancers. The most impressive results have been in patients with Hodgkin's disease, a neoplasm of the lymphatic system.

The basic principle in the curative use of radiation for cancer is also to encompass the total tumor mass and its extensions within the field of radiation at doses that will destroy the cancer but allow the normal tissues to survive or to recover. It is obvious that the limitation of this method is similar to that of surgical resection: the cancer is curable only if it is destroyed entirely by being within the field of radiation at levels lethal to the cancer. Another form of energy, the laser beam, also can destroy superficial cancer, but is not useful in deeper tumors.

The deadly character of cancer lies in its ability to spread and to seed its cells in distant organs of the body. These metastases often exist as microscopic colonies when the patient is undergoing treatment for a cancer that clinically is presumed to be still localized. For these patients, methods of treatment that do not include the whole body will not be successful. Chemical bullets that would selectively hunt out and destroy cancer cells, or in some way provide the body with the ability to render such cells harmless, is the only answer to this problem.

Chemotherapy is a term and concept introduced at the turn of the century by Paul Ehrlich of Germany in his successful attack on syphilis. Since 1960, chemotherapy has gained a place in the treatment and management of cancer, and has given birth to a specialty group of internists, medical oncologists.

The table on page 21 lists some of the drugs that are useful against some forms of cancer in man. The best results, including clinical cures in a proportion of patients, are obtained with rapidly proliferating cancers. Choriocarcinoma, a cancer that arises in the products of conception in women, is an early member of this select group. Roy Hertz and his co-workers at the National Cancer Institute showed its responsiveness to methotrexate, so that more than half of the women with distant mestastes remained well 5 years later.

The present mode of chemotherapy treatment, based on studies of the cell cycles of the tumors and the metabolic pathways of the drugs, combines several chemicals in systematic courses, or the drugs may be combined with X-ray treatments or surgery. The use of cancer-destroying drugs following surgery, called adjuvant chemotherapy, aims to destroy cancer cells that may be present beyond the area of surgical resection.

The removal of the ovaries or testes, or of the adrenals and the pituitary gland produces improvements and temporary regressions of a proportion of advanced cancers of the breast and of the prostate. The effects can be reproduced by giving patients large doses of male or female sex hormones.

The beneficial results of the removal of ovaries in younger women with advanced breast cancer were reported by the British surgeon, George Beatson, in 1896. The effects of removing testes or giving female sex hormone to men with advanced cancer of the prostate were discovered by Charles Huggins in 1936, for which he shared the Nobel prize in medicine in 1966.

The victories of chemotherapy over the more common forms of cancer still lie in the future. But there have been enough real effects to maintain high optimism that this is the practical approach to the clinical problem of cancer. However, at this stage our optimism must be carefully held in check. It is tragic to hear that a patient has decided not to undergo surgery or radiation because a chemotherapeutic discovery may be just around the corner. No one can tell when such a discovery might take place, and it would take years to establish that the initial promising responses were indeed valid or lasting. By that time, the immediate problem of the patient with cancer now would be only of historical interest.

CHEMOTHERPY OF SOME ADVANCED CANCERS

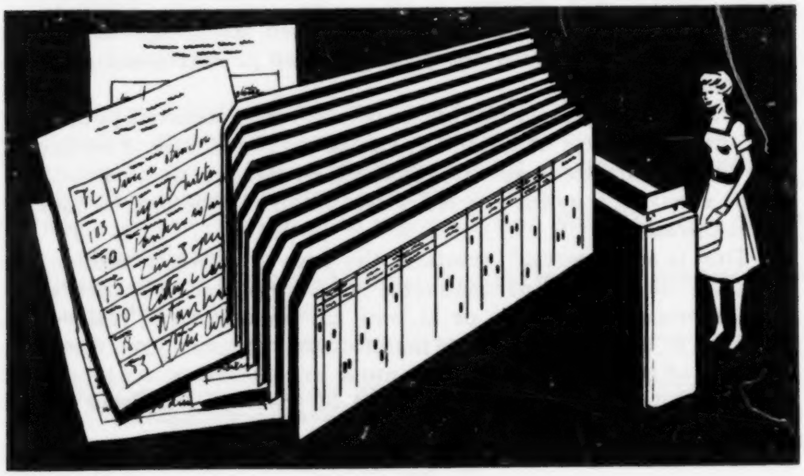
Type of Cancer	Drugs (usually combinations)	Results (percent)
Prolonged Survival or Cure		
Choriocarcinoma (women)	Methotrexate, dactinomycin, vinblastine	90 remission 60 cured
Childhood leukemia (lymphocytic)	Daunorubicin, prednisone, vincrisine, 6-mercaptopurine methotrexate, BCNU, L-asparaginase	90 remission 50 cured
Hodgkin's disease	HN2, vincristine, prednisone procarbazine, bleomycin, adriamycin, vincristine, vinblastine	70 respond 40 survive 5+ years
Testicular cancer	Dactinomycin, methotrexate chlorambucin, cisplatin	90 respond 20 survive 5+ years
Wilms' tumor	Dactinomycin with surgery and radiotherapy, vincristine	30-40 survive 5+ years
Neuroblastoma	Cyclophosphamide, adriamycin, vincristine, procarbazine	50 respond 20 survive 5+ years
Alleviate Severity and Probably Prolong Life		
Prostate	Estrogens, castration	70 respond
Breast	Androgens, estrogens, 5-fluorouracil, vincristine prednisone, methotrexate, adriamycin, tamoxifen	20-40 respond
Acute myelocytic leukemia	Arabinocide, daunorubicin, prednisone	60 respond
Chronic lymphocytic leukemia	Alkylating agents, prednisone	50 respond
Osteogenic sarcoma	Methotrexate, adriamycin	20 respond
Alleviate Severity With Uncertain Prolongation of Life		
Chronic myelocytic leukemia	Busulfan, hydroxyurea, 6-mercaptopurine	90 respond
Multiple myeloma	Alkylating agents, prednisone, vincristine	60 respond
Ovary	Alkylating agents, cisplatin	30-40 respond
Endometrium	Progestins	25 respond

Modified from Krakoff, CA 27:130, 1977

5. The outcome of cancer

End results and clinical trials

One of the unpleasant things about cancer is its tenacity. It hangs on, to reappear years after it is removed and the patient presumably cured. Even in 1878, when Alexandre Von Winiwarter summarized the results of the German surgeons, it was realized that patients had to be observed for several years before conclusion could be reached that a successful procedure had been carried out. An arbitrary 3-year period was accepted as a minimum during which patients should be followed, and this was soon increased to 5 years because experience showed that 3 years was an inadequate period for conclusions about the eventual fate of the patients. For some cancers even this period is not long enough, and an indefinite length of time for periodic examinations is now recommended. Physicians are reluctant to speak of "5-year cure," and prefer the longer but more noncommittal and realistic expression of "5-year survival without clinical evidence of disease."



What has been this experience? What has been achieved with the use of surgery, radiation and chemotherapy in the treatment of cancer?

Our most satisfactory information on these points comes from the registry of all cancer patients in the State of Connecticut, which has been maintained since 1935, and the collection and analysis of records on cancer patients by the National Cancer Institute. This program gathers records from more than 100 selected hospitals in the United States.

We are doing a bit better in the salvage of patients with cancer, year by year. In 1935, approximately 25 percent of all patients with cancer were alive 5 years later. Now the proportion, corrected for other causes of death, is 40 percent.

Analysis of the records shows that this improvement cannot be attributed to better treatment alone, but also reflects earlier awareness of the disease. This is particularly true for cancer of the uterine cervix and for cancer of the mouth. Increased survival of cancer patients is due to better results in the treatment of a few sites of cancer: this is especially true of cancer of the rectum and large intestine, in both men and women, cancer of the body of the uterus as well as of the cervix, cancer of the larynx, and of the thyroid. The results in cancer of the esophagus, of the stomach, of the lung, and of the brain, unfortunately remain dismally stable and dismally low. The table on page 25 summarizes some of these findings.

Only for cancer of the skin can we be reasonably satisfied with our results. The end results in cancer could be further improved, perhaps to the level of 50 percent survival at 5 years, if our presently available knowledge were truly applied. Such application requires national health systems oriented toward preventive medicine, periodic examinations, and early recognition and effective treatment of cancer, among other diseases.

Tentative steps in this direction have been taken, but encounter massive problems of finances, personnel, and physician and patient acceptance.

Skeptical but thoughtful critics of end-result statistics point out that the true effects of treatment can be measured only if we know how similar untreated patients would behave. What proportion of the 5-year survivals, they ask, are really attributable to the natural course of the disease?

This is an important question, the answer to which influences not only the selection of treatment, but our concepts of cancer as a disease process. Is cancer, or at least are some cancers, really not localized at all, but merely one manifestation of generalized disease? The sum of evidence indicates that most cancers do start as a localized process, but it is also true that some of them may become widespread very early.

It is medically and ethically impossible to maintain individuals

FIVE-YEAR RELATIVE[1] SURVIVAL, 1967-1973
(155,434 patients, sex and race combined)

Site	Total	Localized[2]	Regional[3]	Distant[4]
		(percent)		
All sites (except skin)	40	68	38	8
Tongue	33	55	26	13
Esophagus	4	5	2	1
Stomach	13	40	15	2
Colon	45	72	50	8
Rectum	43	68	37	7
Liver	4	10	2	1
Pancreas	2	5	4	0
Larynx	61	78	38	18
Lung and bronchus	9	33	11	1
Female breast	64	84	56	11
Cervix uterine	57	80	45	14
Corpus uteri	75	87	51	19
Ovary	34	78	42	14
Prostate	58	72	61	23
Bladder	61	71	20	7
Kidney	44	70	42	7
Melanoma	67	80	47	13
Brain	29	30	28	—
Thyroid	84	95	83	41
Hodgkin's	60	—	—	—
Multiple myeloma	15	—	—	—
Chronic leukemia	30	—	—	—

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[1] Relative survival is adjusted for expected mortality from other causes for age of patient. Observed rate for all sites was 33 percent.

[2] Localized cancer is limited to the site of origin.

[3] Regional cancer is spread to regional lymph nodes, adjacent organs or tissues, or both.

[4] Distant cancer had spread farther than the regional involvement, or having distant metastases.

Source: Demographic Analysis Section, Biometry Branch, National Cancer Institute. Unpublished, 1979.

with cancer as "untreated controls," as is required in laboratory studies with animals. The few instances of people who refuse treatment for religious and other reasons are seldom representative of the whole population of cancer patients. Nevertheless, there are available some older observations, particularly from England and from Massachusetts, that demonstrate the inexorable course of cancer in man. The course can be slow, especially in certain types of cancer. Cancer of the breast, is the best example, for almost 20 percent of the women who have no definite treatment are alive 5 years later; of course, they are alive with actively growing cancers. In cancer of the rectum, of the urinary bladder, and of the uterus, 5 to 10 percent of patients survive for 5 years or longer without definite treatment. In any compilation of 5-year end results, therefore, a proportion that may be as high as 10 percent is due to the natural duration of this group of chronic diseases rather than to the beneficial effects of treatment.

We also know that rarely there occurs a remarkable "spontaneous" recovery from cancer. By the time cancer is clinically diagnosed, such events have been estimated to happen only once in perhaps 100,000 patients. For practical reasons, therefore, recovery from cancer without surgical or radiation treatment is too rare to have significance. But the theoretical implications of such observations are important. If we understood better the circumstances of these rare cancer regressions, we would be in a position to attempt to produce them under experimental conditions and, eventually, in patients.

In cancer, which is fatal unless its course is interrupted by definitive treatment, the most obvious first question in the evaluation of any new treatment is whether it improves the survival of the patients. If the new procedure is not lifesaving, it may still be useful in producing temporary arrest of the disease, or clinical improvement of the patient by removing distressing symptoms. And even increased survival should be achieved at a reasonable price of risk and morbidity, so that the life that is saved is worth living.

Comparisons of the results of several hospitals or of different surgeons do not give entirely satisfactory answers. This is because patients that enter different hospitals may be quite different in many ways, and because different surgeons may select patients for treatment by using quite different criteria. The greatest single factor that influences curability in cancer is its extent, which is measured by "staging." Stage 1 means that the cancer is localized; stage 2, that there has been regional spread; and stage 3 connotes dissemination. Many types of cancer have special staging schemes, based on clinical and surgical criteria, which are standardized by national and international groups of experts. A surgeon who excludes patients with stage 3 disease obviously is going to have better end results than a surgeon who includes all patients. Hospital and regional tumor registries, which have information on all patients, are sources of end results data, that can be used in comparisons of treatment results.

Evaluation of treatment methods requires careful comparison of the treated patients with *comparable* patients who are not treated, or treated in some other fashion. Pierre Louis of France in 1835 examined the value of bleeding in acute infections by comparing patients who were bled with those who were not. There was no difference in recovery among the two groups, and Louis concluded, by the use of his "numerical" method, that there was no value to bleeding. It was only recently that similar approaches were evolved into statistically sophisticated clinical trials. Bradford Hill was one of the pioneer British leaders in this work.

The controlled clinical trial is now recognized as the scientific method by which the value of new drugs must be tested before such drugs are released for general use. The same method should also be applied to time-honored treatments, many of which are supported more by tradition than by demonstrable facts. A case in point is the place of the radical operation for breast cancer, which in controlled clinical trials was no more effective than less extensive operations.

As more patients with cancer are successfully treated, rehabilitation becomes increasingly important. The classical physical needs were for voice restoration following the loss of the larynx, the voice box, maintenance of colostomy following rectal resection, and muscle training following mastectomy. Behavioral and social readjustments are as essential as physical ones. Rehabilitation socially is made difficult by the reluctance of employers to hire individuals with a history of cancer treatment.

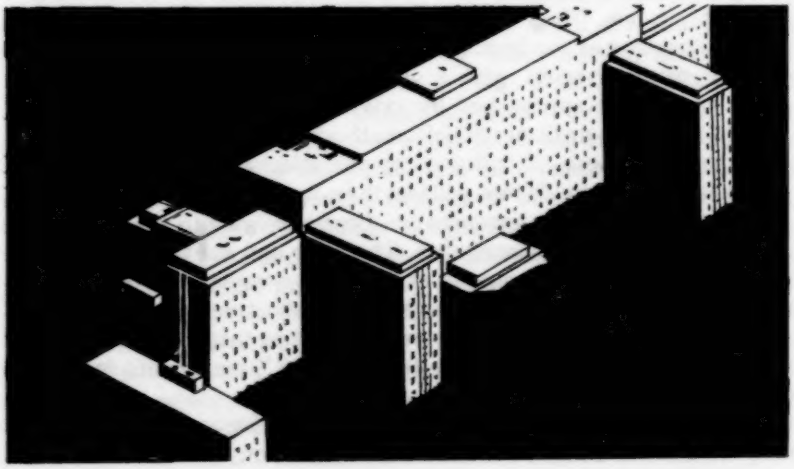
6. Weapons against cancer

Men, material and the scientific method

In the preceding five chapters we have discussed the broad extent of the cancer problem, and what we can do now for cancer as it appears as a clinical problem. Even now, approximately 40 percent of all patients with cancer are being saved, and this fraction could be raised perhaps to one-half by the full application to the whole population of all that is known and all that can be done. Even under such utopian conditions, however, 50 percent of the patients would be doomed to die of cancer, unless and until new knowledge and methods become available through research.

Our victories over cancer up to now have been small but real, and hard won. Moreover, they represent only temporary campaigns toward the eventual goals of prevention and cure of cancer by methods that are simpler and easier than those available at present.

Before indicating how we can aim for these goals of the future, we should examine what has been achieved and how it has been



achieved up to now. For, as Lord Byron wrote, the best prophet of the future is the past.

Our technological advances of the past and of the future depend upon the exercise of a human thought and action process we call scientific research. This approach of man to the world outside of himself was known to the ancient Greeks, and the modern era applied the methods to the world within ourselves with equal effectiveness. In the early 17th century Francis Bacon attempted to codify scientific method as observation, induction, deduction and verification.

The scientific method really is not a limited number of didactic steps, but a continuum of observations, specific questions, hypotheses, tests of validity, and conservative conclusions that are again put to further tests and that give rise to further hypotheses. Thus, the endpoint of scientific research is not only the answer to some specific question, but further questions that can not even be intelligently phrased before the antecedent research is completed.

Scientific research can be usefully divided into observational research and experimental research. In the former, man and his methods can only interpret phenomena as they reach him, without ability to manipulate the phenomena. This is the case for astronomy, for example. This is also the case for epidemiologic studies, in which relationships of various factors are sought in populations, or for pathology studies in which morphologic appearance of tumors is related to the eventual clinical course of the patient. In experimental research, the investigator is in an area where the methods and the materials available to him allow the purposeful selection and creation of situations and appropriate comparative controls.

Attempts are made to divide science into basic and applied branches. Louis Pasteur wrote about this issue as follows: ". . . there does not exist a category of science to which one can give the name applied science. There are science and the applications of science, bound together as the fruit to the tree which bears it."

All research starts with a question, and unless the question is clear and can be approached by existing methods, the research is at least premature until applicable methods are developed. The question, or hypothesis, is followed by the selection of the appropriate materials and methods that will test the question. Science is quantification, and much of its advances are directly related to the mechanical tools that assist in measurement. The ruler and the thermometer are still as important instruments as the most complex electronic apparatuses. Yet science is much more than a collection of measurements. Rearrangement of facts into new patterns, or into what Copernicus called "theories more pleasing to the mind," may result in revolutionary new concepts.

It is also important to recognize what science is *not*. It is not authority, it is not opinion, it is not tradition, and it is not testimonials. Its impudent questions always have been: what is the evidence; what are the conditions under which I may anticipate the same results; what are the quantitative values? Show me!

The source of scientific advances is, and always will be, the individual scientist with a new idea. The individual scientist, however, is usually in the environment of other scientists and libraries, and functions best when continual exchange of ideas occurs. New ideas often arise in an unpredictable fashion, ignited by the confrontation of some unforeseen event by a prepared mind. This event has acquired a coined word to describe it, serendipity. It is interesting to reflect that in extremely well-planned experiments, the chance of unpredictable events is reduced to the minimum, whereas this chance is increased in less planned situations. In experimentation, there is a happy medium that needs to be sought, for in an entirely haphazard set of events, no event stands out as unusual and the opportunity for serendipity again disappears.

Scientific discovery is not a smooth, rational continuum, but a stops-and-starts process in which personalities and unpredictable occurrences, including plain accidents, have a significant role. Scientific work sighted on any target depends upon the availability of appropriate materials and methods, many of which are developed for reasons that may be distant to their eventual application. The "state of the art" is probably the most important single factor for further progress.

Many of the accepted attributions and recognitions in scientific discovery can be questioned by careful examination of even the published record. Priority is often an illusion; progress in science usually depends upon many efforts of many people.

The interdependence of many so-called disciplines in science is forcefully demonstrated in cancer research. The most effective enterprises have been those in which many disciplines and specialities were intimately and meaningfully harnessed. The needs of research are the same as for any other human activity—men, money, material, and time. These elements must be blended into effective forces through planning and management. Cancer research is no exception. Since 1937 the United States has been in the forefront of research directed against cancer because the public and its representatives have supported the activities, allowing expression of research as guided by councils of scientists and science administrators.

In the United States, two organizations, one governmental and the other voluntary, have primary responsibility for leadership and for support of cancer research. The National Cancer Institute was established by an act of Congress in 1937, and expanded by the National Cancer Act of 1971. The American Cancer Society is a voluntary public agency which was incorporated in 1945 but goes back to the Women's Field Army of pre-World War I days. Funds for cancer research and related activities now exceed $1,200 million per year.

Among the larger institutions devoted entirely to cancer are the National Cancer Institute, a component of the National Institutes of Health in Bethesda, Md.; the Roswell Park Memorial Institute in Buffalo, N.Y.; the Memorial Sloan-Kettering Cancer Center in New York City; the M.D. Anderson Hospital and Tumor Institute in Houston, Tex.; and the Sidney Farber Cancer Institute in Boston, Mass. Many universities and medical schools have strong cancer research programs. The cancer program activated by the National Cancer Act of 1971 created additional cancer centers. These centers provide coordination and leadership within their geographic regions to assure the availability of the best care for patients with cancer. They also coordinate and carry out educational, clinical and research activities in the detection, diagnosis and treatment of cancer.

The interest in cancer is world wide, and several other countries are strongly represented in cancer research. In England, the many contributions of the Imperial Cancer Research Fund, and of the Chester Beatty Research Institute in London have been outstanding since the turn of the century. In the Soviet Union, the Academy of Medical Sciences emphasizes cancer research, and has two large institutes devoted to cancer: the Institute of Experimental and Clinical Oncology in Moscow, and the Oncology Institute in Leningrad. The Gustav Roussy Institute near Paris, the Japanese National Cancer Institute in Tokyo, and the Tata Memorial Institute in Bombay indicate the international interest and concern with the cancer problem. The International Agency for Research on Cancer (IARC) in Lyon, France, is an increasingly active and important center for international cooperation and programs.

National and international meetings, symposia and scientific journals help to keep open the lines of communication between scientists; every 4 years there is an international cancer congress, organized by the International Union Against Cancer. An international cancer research data bank has been developed, to help reduce the time-lag in transmission of information between scientists and clinicians.

Animals with cancers, particularly in well-controlled laboratory species, are research materials of inestimable value to cancer research. In fact, cancer research became possible with the discovery, late in the 19th century, that cancers could be inoculated and grow in related animals.

Geneticists, by means of selective inbreeding, developed many strains or families of mice, rats, and guinea pigs that are as identical as twins, and have predictable occurrences of certain types of cancer. Inbred animals, carefully maintained in special laboratory centers, are as valuable to biologists as are pure chemicals to the chemist.

Cancers in laboratory animals are of three types: the spontaneous tumors, induced tumors, and transplanted tumors. The term "spontaneous" is a misnomer, since all it means is that these tumors arise in the animals without known cause, such as an injection of a cancer-producing chemical. As Wilhelm Hueper formerly of the National Cancer Institute stated, cancer, like all other disease, is not a mysterious phenomenon of spontaneous creation but the result of the action of definite chemical and physical, animate or inanimate, endogenous and exogenous pathogenic agents.

Induced tumors differ from the spontaneous tumors only in that some known agent or procedure was introduced, to which the cancer is then attributed. They are, therefore, tumors of known etiology. We can now produce practically any human-type cancer in some experimental animal.

Transplanted tumors should be distinguished from the spontaneous and induced tumors because they represent a different biological system. The host-tumor relationship in the transplanted tumor system may be, and often is, quite different from the relationship between the host and the spontaneous or induced tumor that develops from the tissue of that individual animal.

Cancer research requires all of the exquisite laboratory equipment that typifies modern biomedical research. Electron microscopes, chemical analytical apparatuses, electronic computers, and tissue culture equipment imply a strong industrial potential and technologic skills of high order. These features also require coordination through standards, and are in turn influenced by the complexities of modern civilization. Biomedical research is of national importance and must compete for priority with other national requirements.

Cancer research of course includes studies on human beings. All major cancer research institutions have clinical as well as laboratory departments. The ethical and moral questions regarding the use of human participants in research will continue, but there is agreement that such participation must be voluntary and informed.

Most cancer research institutions also have epidemiologists and statisticians, and are becoming increasingly involved in community problems. The delivery of comprehensive medical care to the population is essential if cancer is to be controlled. Equally essential is an informed, motivated population, educated in health maintenance, awareness of health problems, and how to gain access to medical resources. The economic, social and psychological aspects of medical care systems are becoming recognized as yet another important area for research.

It is the general scientific consensus, clearly indicated not in words but in the efforts that are being expended, that cancer is a solvable problem. The general directions of the profitable lines of attack also have been agreed upon. These include the studies on the causation of cancer by chemical and physical agents, viruses, and their interactions. Knowledge of causation provides leads toward prevention. The second line of research is on the nature of cancer, including the study of the structure and of the intracellular mechanisms that characterize cancer, which may provide us with the necessary leads toward the treatment and prevention of cancer by interfering with these mechanisms.

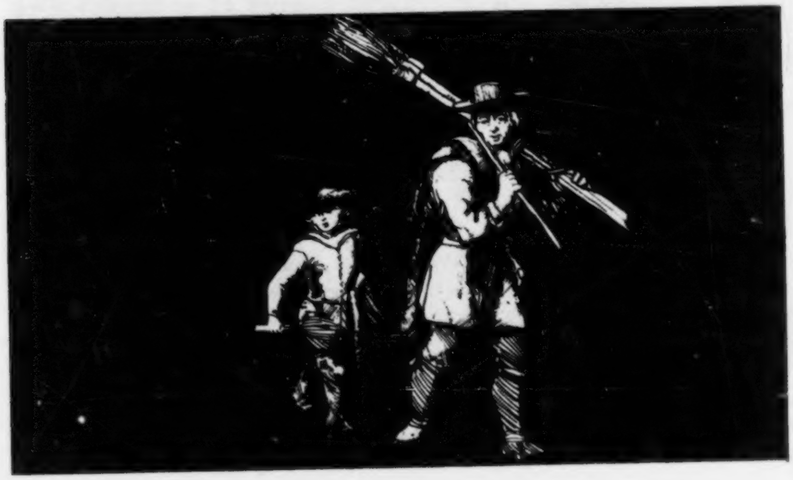
Where, then, do we stand on these research fronts, as of today?

7. Environmental hazards

Chemicals that produce cancer

In 1775, a prominent English surgeon, Percivall Pott, broke a leg and spent his time of recovery writing a book on his observations. He devoted a few pages to the subject of cancer of the scrotum in chimney sweeps, which he attributed to long exposure and intimate contact with soot. This was the first clear description of cancer related to occupation. During the industrial revolution of the 19th century, several additional examples of occupational cancers were identified.

The father of cellular pathology, Rudolph Virchow of Germany taught that chronic irritation was a cause of cancer, and this was considered to be the common denominator of these industrial cancers. Better hygienic measures, stimulated by appropriate legislation, led to the reduction of the industrial problems. Attempts to reproduce cancers in animals with some of the suspected materials were unsuccessful, as the medical literature of the early part of this



century attests. In 1915, however, two patient Japanese investigators, Katsusaburo Yamagiwa and Koichi Ichikawa continued to paint the ears of rabbits with tar for many months, and were rewarded by the conclusive development of skin cancers at the site of application of the tar. By 1933, British scientists under the leadership of Ernest Kennaway isolated a pure chemical, benzopyrene, from tar, and showed that it produced cancers at the site of application in mice. This polycyclic hydrocarbon, beautifully fluorescent under ultraviolet light, was one of a large series of chemical compounds that readily produced cancers of the skin or of the subcutaneous tissues in laboratory rodents.

Particular excitement was aroused when a carcinogenic hydrocarbon was made in the laboratory from desoxycholic acid, a component of bile. It was suspected that cancers could be due to the synthesis by the body of carcinogens from cholesterol and other steroid chemicals. There are many such chemicals in the body, including sex hormones and hormones of the adrenal gland. These optimisms soon foundered because such chemicals could not be found and because many other, unrelated chemicals were added to the list of carcinogens, or cancer-producing chemicals.

In rats of certain strains, a single oral dose of a powerful carcinogenic hydrocarbon, DMBA, is quickly absorbed so that within a few hours DMBA is found in every tissue of the body. Yet the cancer reactions are limited to a few types and sites, which are different in animals of different age and sex. In very young rats, subcutaneous sarcomas are elicited; in mature females, breast cancers; in males, cancers of the skin and sebaceous glands. Thus, the susceptibility of the end-organs to carcinogenesis varies, and the limited responses suggest specific, dynamically changeable reaction sites in various tissues.

Japanese workers also introduced a series of amino-azo dyes that on feeding to rats gave rise to liver cancers. The prolific chemists expanded the list of cancer-producing chemicals to several hundred, including many of unrelated structure insofar as chemical configuration was concerned. The chemical structures of some carcinogens are given in figure 4 on page 37. The search for a simple relationship between chemical structure and cancer-producing activity was replaced by more sophisticated investigations of the mode of action of the chemicals.

The ubiquitous hydrocarbons can be identified in a wide variety of tars, oils, soots, and products of incomplete combustion of vegetable material such as the smoke of trash and tobacco, burnt coffee beans, and the deposits on smoke-preserved meat and fish. With the aid of radioactive isotope labels in the structure of the chemicals, it was shown that they were eliminated primarily through the gastrointestinal tract. The azo dyes are eliminated from the body primarily in the urine, after metabolic changes in the liver. The

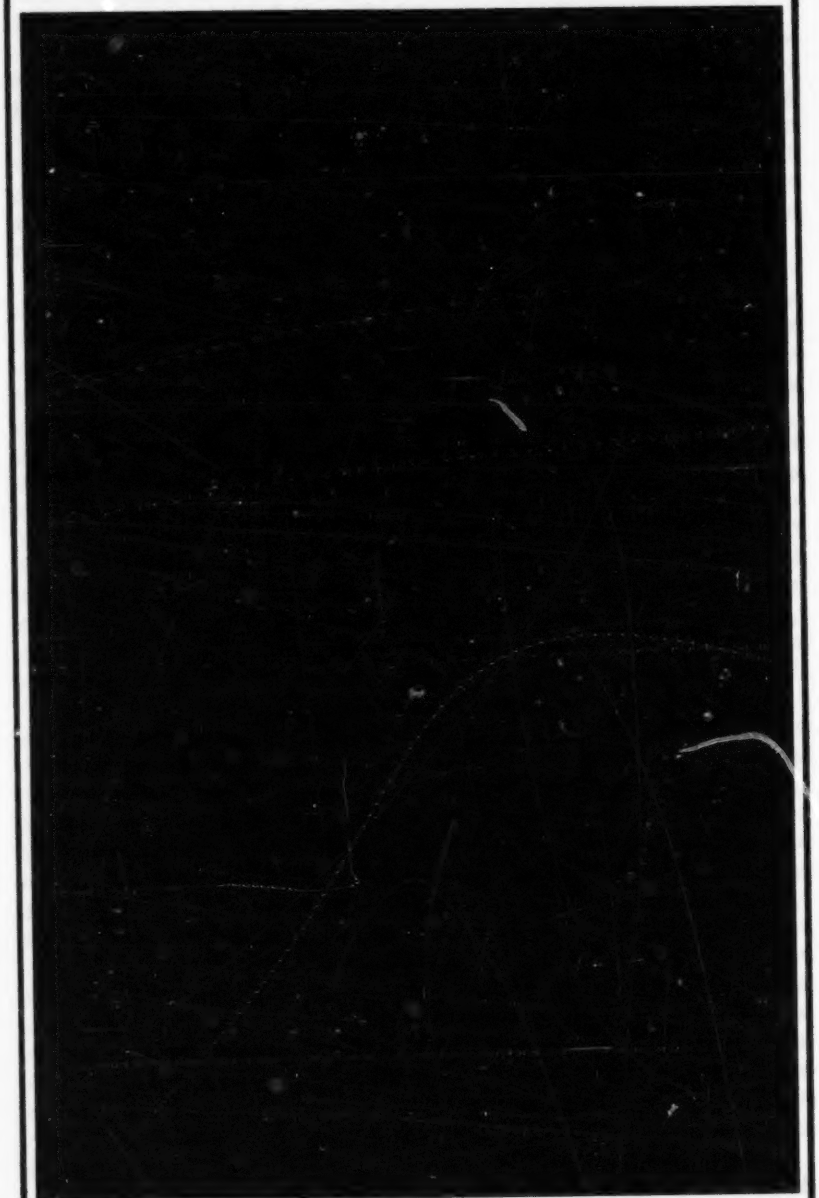


Figure 4. Chemical structure of some carcinogens.

compounds have the property of binding tightly with tissue nucleic acids and proteins.

The female sex hormones, including artificial compounds with estrogenic activity such as diethylstilbestrol, produce a wide variety of cancers in rodents, at sites distant to application but in tissues that respond physiologically to these hormones. The list includes cancers of the breast, the testis, and the uterus, and an increase in the occurrence of leukemia. The reactions occur in certain inbred strains of mice and not in others, indicating the importance of the genetic background of the animal.

Nitrosamines, carbamates, and alkylating agents such as nitrogen mustard, are among chemical classes that include carcinogens. Nitrosamine compounds are of particular interest, and their presence in foodstuffs may be of importance to man. Cancers of the esophagus, stomach, and colon have been produced by nitrosamines in dogs as well as in rodents.

With crude mixtures of materials such as tars, which contain many irritating chemicals, an inflammatory reaction at the site of application is almost inevitable. With pure chemicals in small doses, however, cancers may arise without evidence of preceding inflammatory changes. Also, many irritating chemicals that destroy tissues do not possess the property of evoking cancers, thus separating the response of carcinogenesis from that of inflammation.

It was noted that tars with very small amounts of cancer-producing chemicals were more effective in producing cancers than the pure chemicals themselves. This indicated the presence of other compounds in the mixture that accelerated or stimulated the reaction, which Murray J. Shear called *cocarcinogens*. I. Berenblum of Israel extended this concept in a series of ingenious experiments. Mice painted just once with a powerful carcinogenic hydrocarbon did not develop cancers, but if the same skin site were painted months later with croton oil, a material usually without carcinogenic activity, cancers promptly appeared.

The present concept regarding the induction of cancer is that the process goes through several distinct steps. The first one, called *initiation*, is produced by a carcinogen, and probably involves sudden, irreversible mutational changes. Subsequent growth and development of an actual cancer require *promotion*, which may be the result of additional applications of a carcinogen, or of other, noncarcinogenic materials. Promotion of cancer may involve additional steps within the cells, or the reduction of tissue and host protective mechanisms.

Another complication was introduced by studies with urethane, a simple carbamate that was found to produce lung tumors in mice. Urethane does not produce skin cancers in mice even after prolonged application to the skin or after ingestion. But if mice that are fed urethane have their skin painted with croton oil, cancers of the skin are produced. Thus, urethane is an "incomplete" carcinogen for the skin, requiring the addition of a cocarcinogen to complete its reactions.

Important contributions to the understanding of carcinogenic action have been made by two husband-wife teams of investigators, the Millers of Wisconsin, and the Weisburgers of Bethesda, working with cancer-producing chemicals of the azo-dye and of the fluorene type. One of the latter, 2-acetylaminofluorene, was suggested for use as an insecticide, but studies on its chronic toxicity in rats showed that it produced a wide variety of cancers. This stopped its economic development, but led to its use as a tool in cancer research.

Studies with isotopically labeled acetyl-aminofluorene showed that the rat converts the chemical into a hydroxylated metabolite in the liver, and that this metabolite rather than the parent compound was the active carcinogen. Guinea pigs given the compound over protracted periods failed to develop tumors and metabolic studies showed that this species did not hydroxylate the chemical. In rats, single doses of acetyl-aminofluorene are ineffective in evoking cancers; the compound has to be given over a period of several weeks in order to produce carcinogenic reaction. This was elucidated by finding that the necessary enzymes in the liver for the hydroxylation of the compound are not present until the animal is exposed for some time to the compound. In effect, an enzyme had to be mobilized by the animal to meet the toxic challenge of the chemical, but this defense reaction had the harmful effect of producing metabolites that are carcinogenic.

The metabolic participation of the host in carcinogenic reaction was also demonstrated for the polycyclic hydrocarbons. When mice are given small doses of carbon tetrachloride before being injected with a carcinogenic hydrocarbon, many more tumors of the lung are produced than with the same dose of hydrocarbon alone. Carbon tetrachloride injures the liver, which is involved in the detoxification and the elimination of these compounds from the body. The animals with damaged livers were less able to protect themselves against the hydrocarbon.

Carcinogens, therefore, include many types of compounds that act in different, complex ways. Some produce cancers at the site of contact, perhaps by direct, specific injury to the cells. Others produce cancers at distant sites. Some require metabolic conversion for activity, others are incomplete in their action and are potentiated by still other chemicals. Still other groups of chemicals are not carcinogenic, or very weakly so, but either stimulate or complete reactions initiated by ineffective dose levels of carcinogens.

The discovery of carcinogens such as benzopyrene led chemists to synthesize many related chemicals in order to study the relationship of chemical structure to biologic activity. Minor chemical changes in the molecule may convert an active carcinogen into a chemical that is completely devoid of this activity. Simultaneous injection of a carcinogen and a closely related inactive chemical relative often prevents or retards the action of the carcinogen. The interpretation of the finding is that the inactive chemical competes for the same attachment groups within the cell that are required for the carcinogenic change.

There are also chemicals that by several mechanisms inhibit or delay cancer; they are the anticarcinogens. Retinoids, related to vitamin A, prevent experimental cancers in rodents. Antioxidants, chemicals that block reactions of substances with oxygen, such as butylated hydroxytoluene (BHT), also inhibit the formation of chemically induced cancers. Vitamin E and selenium are also involved in antioxidant reactions and exert cancer-inhibiting effects.

Drugs, food additives, cosmetics, and insecticides are among the many exposures of man to new chemicals. Tests for safety of such products include tests for carcinogenic activity. Tests for carcinogenic activity have to be done on animals, and how these can be extrapolated to man is a most vexing question.

Cancer-producing chemicals are not limited to industrial products. They also occur in nature, in plants and in molds. The nut of the *Cycas circinalis* palm, used as food in some Pacific islands, contains a compound, cycasin, that produces cancers of the kidney and other organs in rats. Bracken fern *(Pteridium aquilina)*, eaten by cattle, produces bladder cancer.

The alkaloids of *Senecio jacobaea*, a plant used by African natives in diet, and chili peppers, lead to the development of liver cancers in rats. These and similar sources of cancer-producing materials from plants may play a role in the occurrence of some cancers in man.

Strains of a common mold, *Aspergillus flavus*, which grows on wet peanuts and corn, make a group of lactone-type compounds called aflatoxins. The compounds are very destructive to the livers of fowl, especially ducklings and turkeys. When fed to rats, they produce cancers of the liver. The chemicals are among the more active carcinogens for the liver, producing their effects at doses of a few micrograms. Molds and bacteria growing on food products used by man represent another source of environmental carcinogens.

Interest in chemicals that produce cancer started with observations on man, and the laboratory investigations lead us back to man. In human populations, long-term exposure to pure chemicals is relatively rare; usually such chemicals are a part of complex mixtures, and usually the people are simultaneously exposed to other complex environmental factors as well. Studies of occupational groups, or of groups exposed to unusual environmental situations because of habit or habitation, have established an impressive list of carcinogenic hazards for man. Some of these carcinogenic chemicals are listed in the table on page 41.

SOME CHEMICALS CARCINOGENIC FOR MAN

Agent	Site of Cancer
Polycyclic hydrocarbons	
Soot, tar, oil	Skin
Tobacco smoke	Lung
Aromatic amines	
2-naphthylamine, benzidine and derivatives	Bladder
Alkylating agents	
Mustard gas and derivatives	Lung
Melphalan and analogues	Bone marrow
Asbestos	Pleura, lung
Arsenic	Skin, lung
Benzene	Bone marrow
Vinyl chloride	Liver
Chrome ores	Lung
Nickel ores	Lung, nasal sinus
Isopropyl oil	Nasal sinus
Estrogens	Uterus, vagina
Phenacetin	Kidney, pelvis
Immunosuppressive drugs	Lymphatic system

Among the effects of industrial exposures that have been demonstrated to increase the risk to cancer are the following: bladder cancer among aniline dye workers that handle 2-naphthylamine and some related chemicals; bone cancer among workers who ingest or inhale radium; lung cancer among workers who inhale chromates, radioactive ores, asbestos, and iron; cancer of the nasal sinuses and of the lung in nickel mine workers; skin cancer among workers handling distillation and fractionation products of coal, oil shale, lignite and petroleum.

Industrial settings are important sources of potentially useful information of immediate applicability to man. Such information is not easy to acquire because careful long-term observations on groups that have considerable occupational turnover are required.

Hazards to which certain occupations are exposed have more general implications to the general population of the area. Industrial wastes are discharged into the air and into the waters of the community, and represent potentially important sources of additional carcinogenic hazard.

Among the environmental, occupational cancers that are unknown in the United States is the centuries-old epidemic of bladder cancer in Egypt, among the peasants that toil in the waters of the

Nile infested with a fluke, *Schistosoma haematobium*. The parasite enters the body through the skin, and eventually encysts itself in the bladder wall, producing chronic changes that may eventually terminate in cancer. In 1972, Robert Kuntz and his associates at the Southwest Research Institute in San Antonio, Texas, reported that several species of monkeys infected with the parasite developed bladder cancer. The road is now open toward defining the disease process and testing of methods that might help to control this serious affliction of man.

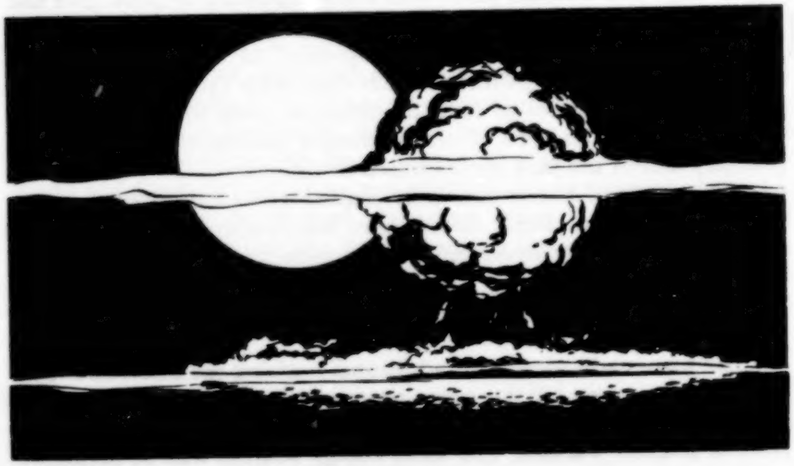
8. Radiant energy

Sunlight and atomic bombs

Among the cancer-inducing stimuli of our environment is the very energy source upon which life itself depends, the light of the sun.

The ultraviolet radiation story begins with the clinical observation of Paul Unna of Germany, who in 1894 related exposure to sunlight with chronic skin changes and skin cancer. In 1928, G. M. Findlay of England succeeded in producing skin cancer in experimental animals exposed to intense sunlight. More refined studies by later investigators, particularly Harold F. Blum of the National Cancer Institute, show that this effect was not due to heat and that it could be localized to a relatively narrow band of the wave spectrum. The cancer-producing range is around 3000 Angstrom units (a measure of wave length). It is interesting, and may be significant, that many of the carcinogenic hydrocarbons show a peak of absorption in the same wave range.

The cancer-producing effects of ultraviolet radiation appear to be



limited to the skin, probably because of its low penetration. In thin-skinned animals such as albino mice, sarcomas are initiated as well as other cancers. Studies on human populations show convincingly that skin cancer, especially the squamous epitheliomas, are induced by ultraviolet radiation. The incidence of skin cancer is highest in the white population of the southern and western parts of the United States and lowest in the north, and related to the amount of sunshine in the area. This relationship is also evident in Australia. Furthermore, skin cancer occurs more frequently among people who work outdoors, such as sailors and farmers, than among people who can guard themselves against exposure to the sun. The color of the skin is another factor. Cancer of the skin is most common among fair-complexioned people, and much less frequent among Negroes than among the so-called white races. The Irish appear to be particularly sensitive to solar radiation.

The atmosphere shields the earth and its inhabitants from high levels of ultraviolet and other solar radiation. One of the environmental problems we face is the possible consequence of disturbing the atmospheric blanket by supersonic transport and air pollutants.

The discovery of the cancer-producing effects of ionizing radiation from radium and X-rays was made on human beings. The pioneer workers with the new emanations developed dryness, ulcers and, eventually, cancers of their hands. Jean Clunet of France in 1910 produced cancer in a rat following application of radium to the skin. This experimental induction of cancer preceded the discovery that tar produced skin cancer in rabbits, but failed to arouse interest of laboratory investigators.

Ionizing radiation can cause several forms of cancer in man and in animals. Radiologists and others exposed to increased doses of radiation are more liable to develop leukemia than people who are not so exposed. Radium salts, which are deposited in bone, give rise to cancers of bone. A historical tragedy was the death of women from bone cancer following the ingestion of radium by licking brushes they used in painting watch dials with radium. In animals, exposure to high doses of ionizing radiation leads to the occurrence of leukemia, and in mice of certain strains tumors of the ovary, the pituitary and of the lung are increased in incidence.

The people of Hiroshima and Nagasaki who survived exposure to the two prototype atomic bombs have been carefully studied during the past 30 years by American and Japanese scientists. The information leaves no doubt that a single exposure at high doses produces leukemia in man. Also increased was the incidence of cancers of the lung, breast and thyroid.

The man-made sources of additional ionizing radiation undoubtedly represent one of the more serious potential cancer-producing hazards of the future. International maturity, man-kind hopes, will control nuclear warfare. The same energy sources will be harnessed for industrial and other peaceful purposes. Key issues involve the questions of dose and threshold. The effects of radiation are dose-dependent, but some risk appears to extend to the lowest measurable exposures.

The questions of dose and threshold also apply to chemicals with carcinogenic activity. We really have no answer to these questions, nor any reasonable experimental design through which definitive answers can be anticipated. For example, if 1 milligram of a chemical produces cancers in all of 100 mice, and 1/100th of a milligram produces only one cancer in another group of 100 mice, should it be assumed that 1/10,000th of a milligram is entirely safe, or that it will produce one cancer in 10,000 mice? It is feasible to set up an experiment with 10,000 or even 100,000 mice, if necessary, but the trouble would lie in the interpretation. Such a low-order effect would be well into the range of occurrence of "spontaneous" tumors, and its relationship to the chemical would be open to doubt. And there is always the question of how far the findings on one species of animals apply to other species, including man.

An increase in leukemia occurs in children who are exposed to X-rays while still in the uterus, because the mother had required a diagnostic X-ray of her pelvis during pregnancy. At that low dose of X-ray, the risk to leukemia is increased by a factor of less than twofold. Whether this means that an addition of 2 rads (a unit of absorbed radiation energy) to the lifetime exposure of the earth's population will result in thousands of additional deaths from leukemia and other cancers remains in the realm of theory.

All terrestrial life is exposed constantly to radiation from cosmic sources. It is reasonable not to add unnecessarily to the total dose. X-ray exposure for trivial reasons, such as to see whether shoes fit, is to be condemned. X-ray machines should be inspected for leaks. But X-rays are of inestimable value in diagnosis, and there should be no hesitation when they are used for sound and sufficient reasons.

Life is a hazard, and man must always balance one risk against another. In relation to carcinogenic effects of chemicals that may be added to food, a functional decision has been made in the United States and placed on the law books of the land. Provision of the Food and Drug Act prohibits the addition of any amount of cancer-producing chemicals to food. However, what is or is not cancer-producing is decided on the basis of animal tests. The results have to be interpreted by technically qualified committees, which are faced with the exceedingly difficult problems of extrapolating the findings to man.

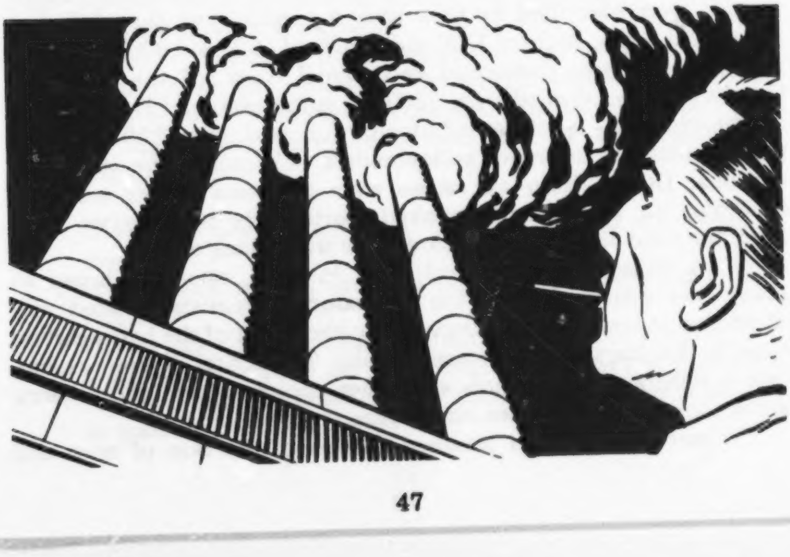
9. The air we breathe

Carcinogens in our atmospheric environment

Our lungs are one of our main contacts with the outside world. We breathe about 20 times every minute, inhaling and exhaling a pint of air with each breath.

When the air we breathe contains impurities, the lungs ordinarily have ways of getting rid of them. This is done by coughing, or by more complicated processes within the lining of the bronchial tubes or of the lung tissue. Excessive exposure to impurities that are inhaled brings about changes in the bronchial linings and the lungs which eventually result in disability and illness. If the impurities contain cancer-producing chemicals, prolonged exposure can lead to cancer.

As early as 1879, German pathologists reported that an important proportion of the high death rate from lung disease in the miners of Schneeberg and Joachimsthal was due to lung cancer, attributable to the inhaling of various metallic ores of that region,



including uranium. Recent studies among uranium miners of the United States also show that radioactive ores have a high carcinogenic potential for the human lung. Other occupational inhalants that have been associated with increased risk to lung cancer include chromates, nickel, asbestos, coal gas, and bischloromethyl ether.

Lung cancer in the United States and in Europe has shown the greatest increase of any cancer site during the past 30 years. It was formerly considered to be a rare disease. There are now over 90,000 deaths per year in the United States from this cause, and it has become the leading cancer killer of men over 40 years of age, and has risen to third place in women. If the present trends continue, it is estimated that about 1 million persons who are now school children will die eventually of lung cancer.

This cancer epidemic is related to two factors. The major one, accounting for over 70 percent of the increase in the United States, is cigarette smoking, with other forms of tobacco having a lesser role. The second factor is air pollution caused by industrial wastes, automobile exhausts and household sources. Nonsmoking city dwellers have up to 3 times more lung cancer than rural nonsmokers. Tobacco smoking is an individual form of air pollution. The identification of cigarette smoke as a major cause of lung cancer and other lung diseases ranks as one of the major scientific discoveries of this century, equivalent to the 19th century discovery of water pollution as a cause of many gastrointestinal diseases such as typhoid.

The first studies on tobacco smoking were of the so-called restrospective type, in which patients with lung cancer were asked about their previous habits, and their answers compared with those of patients with other diseases. Almost all lung cancer patients replied that they had been long-term, heavy cigarette smokers. This answer was much less frequent among patients without lung cancer. The next studies were of the prospective type, in which large groups of men were identified by their smoking habits, and then followed for several years. Richard Doll and Bradford Hill used 80,000 British physicians; Cuyler Hammond and Daniel Horn, of the American Cancer Society, studied over 180,000 volunteers; and Harold Dorn of the National Institutes of Health followed over 200,000 U.S. Government life insurance policyholders. All reached the same conclusions. Deaths from all causes were increased among smokers, according to the amount smoked, particularly if cigarettes were used; the most striking proportional rise was in lung cancer.

With these epidemiological clues in hand, scientists began to study the relationship in the laboratory. Chemists isolated and identified at least a dozen carcinogenic chemicals of the hydrocarbon type in the "tars" from tobacco smoke. The action of these chemicals is enhanced by phenols and other cocarcinogens, and tobacco smoke contains yet further carcinogens.

Tobacco smoke tars produce cancers of the skin of mice and other laboratory animals when painted on the skin for long periods. Cancers of the bronchi have been produced in dogs, following prolonged painting of the bronchi with such tars. Cancers of the lung also have arisen in dogs that were trained to smoke cigarettes through artificial openings in their windpipes.

The membranes lining the lungs absorb cancer-producing chemicals from tobacco smoke. The protective mechanisms by which the lungs rid themselves of impurities are first paralyzed and then destroyed by tobacco smoke. Prolonged exposure of the lungs of animals to tobacco smoke produces changes in cells that resemble early stages of cancer development. These changes are also seen in the lungs of heavy smokers who die of causes other than lung cancer.

Deaths from lung cancer are about six times more frequent among men who smoke regularly in any form (cigarettes, pipe or cigars) than among nonsmokers. Deaths from lung cancer are 60 times more frequent among men who smoke over 2 packs of cigarettes per day than among nonsmokers.

Women smoke less than men, but among them, too, cigarette smoking increases the risk of lung cancer. Among nonsmoking men and women who live in the country, the risk of developing lung cancer is approximately the same. The younger one starts smoking, the greater the risk of developing lung cancer. The risk is reduced by stopping smoking, although it does not return to the low frequency among those who never smoked.

The strong association between lung cancer and cigarette smoking is probably due to customary deep inhalation of the bland cigarette smoke. The more acrid, alkaline cigar and pipe smoke is seldom inhaled deeply into the lungs. Tobacco smoking by workers exposed to asbestos or uranium is particularly hazardous, and significantly enhances the risk to lung cancer. The combination of tobacco smoking and the drinking of alcohol is an important factor in the origin of cancers of the mouth and of the esophagus, the pipe between the mouth and the stomach.

General air pollution, or pollution from industrial sources, is primarily a matter for community action. The problem of smoking is primarily a matter of individual decision. The available facts indicate that the following is sound medical advice to be considered in arriving at the decision:

1. If you are not a smoker, do not start; if you are a smoker, stop.
2. If you must smoke, smoke a pipe or cigars rather than cigarettes.
3. If you must smoke cigarettes, smoke as few as possible (certainly under a pack per day), use filtered low-tar cigarettes, inhale as little as possible, and discard each cigarette as soon as possible.

The health hazards of smoking are not limited to lung cancer. Bronchitis, bronchiectasis, and other crippling lung diseases are produced in even larger numbers. Deaths from heart disease are accelerated and increased. Cancers of the oral cavity, larynx, esophagus and the urinary bladder are associated with the habit. Tobacco smoking is a major health hazard. As such, it requires national consideration of our citizens and our Government.

It is disappointing that 15 years after the facts about the health hazards of tobacco were in, tobacco growing is still subsidized. Every year over 500 billion cigarettes are manufactured, and over 50 million people still smoke them in the United States.

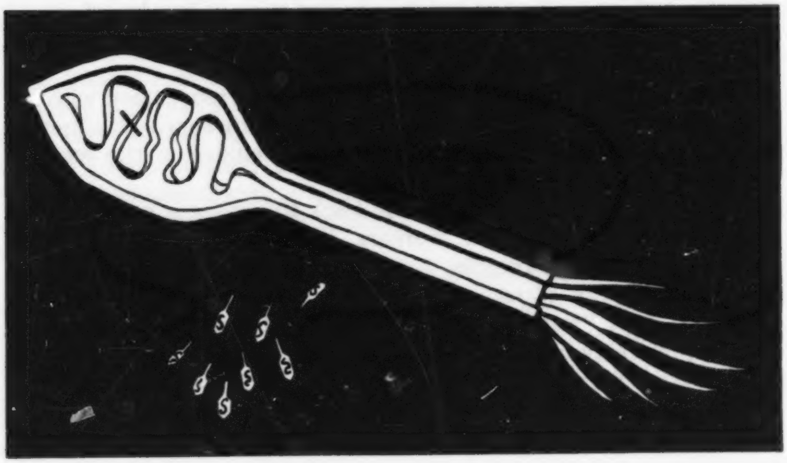
In the final analysis, a change for the better can be achieved only through individual commitment against smoking. "Life-style" that includes nonsmoking is more important for the preservation of health than the medical therapeutic procedures that can be directed against the consequences of the smoking habit.

10. Biological carcinogens

Viruses that produce cancer

Toward the end of the Pasteur era of bacteriology and infectious diseases, cancer, too, received attention. Many bacteria, fungi and other microorganisms were observed, isolated and claimed as causes of cancer. None of these reports was substantiated, and more careful work that avoided incidental contamination was always negative. By 1910 scientists became quite sure that cancer was not caused by microorganisms of any kind. From this was derived the dictum that cancer was not infectious. Even today, some stubborn workers continue to claim that fungi, usually with complex life cycles including filterable phases, produce cancer, but their demonstrations are unconvincing.

The period that closed with the disappointing bacteriological chapter in cancer research coincided with the earliest descriptions of diseases caused by viruses. The credit for this discovery belongs to a Russian, Demitri Ivanovsky, who in 1892 reported the transmission



of tobacco mosaic disease by extracts that had been passed through filters too fine to allow the passage of any known bacteria; thus the term "filterable virus." Several years later, and probably independently, the Dutchman Martinus Beijerinck made almost identical observations.

Peyton Rous of the Rockefeller Institute in New York in 1911 succeeded in transmitting several sarcomas of chickens by means of cell-free, bacteria-free filtrates. The Rous sarcoma virus (RSV) is the first clear demonstration of the role of a virus in one type of malignant tumor. The discovery came at the wrong time, just when the noninfectious nature of cancers appeared to be established. Cancer research swung into a period of preoccupation with genetics, and tar-induced tumors. Only a few workers continued to explore the virus possibilities. Rous shared a Nobel prize 55 years later!

In the period of 1933 to 1937, two important cancer-virus discoveries were made. Richard Shope of the Rockefeller Institute succeeded in passing a wild rabbit papilloma or skin wart to domestic rabbits by means of cell-free filtrates, and in the new hosts the papillomas acquired the invasive characteristics of cancer. As observed with the Rous sarcoma of chickens, the filterable agent was seldom recoverable from the malignant tumor it had induced. In 1936, the workers at the Jackson Memorial Laboratory, primarily geneticists, discovered that the transmission of breast cancer in mice was extrachromosomal, in that it occurred in offspring of mice only if the mother came from the high breast cancer line. If the father came from the high cancer line, the progeny did not develop breast cancers. John Bittner explored one of the simplest possibilities, that something was transmitted from the mother to the young after birth, and found that this something was indeed in the milk of the mothers. By the process of foster-nursing high breast cancer strains by low breast cancer females, the occurrence of cancers was dramatically reduced, and by feeding or injecting young mice of low breast cancer strains with milk from mice of high cancer strains, the incidence of breast cancer could be strikingly increased.

During this period, too, cancer research was preoccupied with the polycyclic hydrocarbons, and the most promising approach appeared to be the biochemical one. Viruses were excluded in the research plans of many important institutions.

Credit for forcing the attention back to viruses is probably due to the discoveries of three workers. Ludwik Gross of New York showed that some leukemias of mice also were transmitted by cell-free filtrates. The filtrates were poor sources of the agents unless they were first "warmed up" by passage in tissue culture, and very young, preferably newborn animals were used for the transfer experiments. Sarah Stewart and Bernice Eddy at the National Institutes of Health, following similar leads, succeeded in isolating from a mouse leukemia another agent that produced salivary gland cancers in mice.

SOME ANIMAL CANCERS CAUSED BY VIRUSES

Date	Investigators	Animals	Cancers
1908	Ellerman and Bang	Chickens	Leukemia.
1911	Rous	Chickens	Sarcoma.
1933	Shope	Rabbits	Skin cancer.
1934	Lucké	Frogs	Kidney cancer.
1936	Bittner	Mice	Breast cancer.
1951	Gross	Mice	Leukemia.
1957	Stewart et al.	Mice to mice, rats, rabbits.	Multiple cancers.
1961	Eddy et al.	Monkeys to hamsters	Sarcoma.
1962	Trentin et al.	Man to hamsters	Sarcoma.
1964	Harvey	Mice	Sarcoma.
1964	Jarrett et al.	Cats	Leukemia.
1965	Hull et al.	Monkeys to hamsters	Sarcoma-lymphoma.
1965	Sarma et al.	Chickens to hamsters	Fibrosarcoma.
1966	Darbyshire	Bovines to hamsters	Sarcoma.
1967	Opler	Guinea pigs	Leukemia.
1967	Sarma et al.	Dogs to hamsters	Fibrosarcoma.
1968	Melendex et al.	Monkeys	Lymphoma.
1968	Graffi et al.	Hamsters	Lymphoma.
1969	Snyder and Theilen	Cats	Fibrosarcoma.
1972	Wolfe et al.	Monkeys	Fibrosarcoma.

On passage through tissue culture the agent acquired even wider carcinogenic properties in being able to produce many different types of tumors, not only in mice but in several other rodents, such as rats and hamsters. This "polyoma" virus broke through all previous reservations against virus research in cancer. Up to then, it was considered that cancer viruses such as the Rous virus in chickens or the Shope virus of rabbits were species and tumor specific. Now both the tumor specificity and species specificity concepts were shattered, and the implications became much wider.

During this period, 1945-1955, virus research was making great strides, especially in its organized attack on the problem of poliomyelitis. Tissue culture, the electron microscope, serological and immunological identification techniques were effective weapons that provided our victory over poliomyelitis. The same weapons were now trained against cancer.

In various animal species, there are now over 100 cancers that are established to be of viral etiology. (See table above.) In addition, there are several benign tumors stimulated by viruses, to indicate a spectrum of proliferative cell reactions. The structure and chemical composition of viruses are now well understood. Studies on the structure of animal cells are beginning to reveal how the virus-cell interactions take place.

The type of cellular reaction produced by a virus apparently depends upon the degree to which the host can resist viral invasion. In many common virus diseases, the endpoint is the destruction of virus-invaded cells. Limitation of viral reproduction and recovery of the host organism depend upon the development of an antibody response. The virus-host relationship in such virus entities as warts leads to the stimulation of cell growth by the virus, but the immune mechanisms eventually gain the upper hand and the lesion is localized or eliminated. In the benign tumors such as the papilloma of the wild rabbit, the fibroma of the squirrel, and the fibroma of deer, there is a more equal balance between the virus and the cells, with slow but controlled growth of the tissue. These tumors contain easily recoverable virus particles. In the true invasive cancers, the causative virus is difficult to recover.

The world of viruses is a large one, and includes entities that are quite different in size and in chemical structure. Basically, viruses are giant molecules of the same chemical structure as the components of animal and plant cells. Viruses are cell parasites in that they can replicate only within animal or plant cells. They are structurally either deoxyribonucleic acids (DNA) or ribonucleic acids (RNA), a series of nucleic acid components (purines and pyrimidines) attached along backbones of sugarphosphoric acid building blocks. The nucleic acids during the extracellular phase of virus existence are contained in a protein coat, which is shed when the virus enters a cell.

There are examples of both DNA and RNA-type viruses among the carcinogenic virus classes. The DNA-types include the "papova" group, an abbreviation-condensation word for the Shope *pa*pilloma virus of rabbits, the *po*lyoma virus of mice, and the *va*cuolating virus of the monkey. These viruses are initially seen in the nucleus of the cells they invade.

The RNA-types are called oncornaviruses, a combination of *onco*genic and *rna*. They include viruses of the lymphoma-leukemia complex, which produce the leukemias of chickens, the Rous sarcoma, and the leukemias of mice, of which there are a dozen or more different varieties. These viruses are initially seen in the cytoplasm of the cells. The Bittner virus, which is required for the occurrence of most breast cancers in mice, is another cytoplasmic RNA virus entity.

As more information regarding viruses and their behavior within the cell becomes available, it becomes increasingly clear that the so-called cancer viruses are not a unique class but represent examples of virus entities that fit them nicely into the whole world of viruses. A common virus that is found in the monkey, the SV40 virus, when grown on tissue culture and injected into newborn hamsters, produces sarcomas at the site of injection. This finding led to considerable consternation among public health officials because SV40 contaminated many of the polio vaccine preparations that were used in immunizing children in 1955. Fortunately, careful observations fail to show any increase in cancers among children who received contaminated preparations, and now such contamination is avoided. Following this lead, John Trentin and his co-workers in Houston, Tex., found that a common virus that occurs in the nose and throat of man, adenovirus 12, also evokes cancers in hamsters after being passed and activated by tissue culture. Several other human adenoviruses also produce sarcomas in hamsters. Thus, under special conditions, rather common viruses were shown to possess cancer-producing activity.

The role of RNA viruses in human cancers is surmised by indirect evidence. Particles resembling type C virus have been described in acute leukemia. Virus-related nucleic acid, protein antigen, and enzyme activity have been detected in some human tumors.

A current candidate for a human cancer virus is the Epstein-Barr (EB) virus, a DNA herpes-type entity, that was isolated from African children with Burkitt's lymphoma. EB virus causes infectious mononucleosis, a benign, self-limiting disease, and appears to be involved in cancer of the nasopharynx as well as Burkitt's lymphoma. Genetic and environmental factors interact with the virus in the progression to cancer. Another possible human DNA virus is herpes simplex (HSV-2) in cancer of the uterine cervix. The possible role of hepatitis B virus in liver cancer is another example.

There is probably no single "cancer virus." Oncogenic viruses appear to become part of the genetic material of cells, where they can exist in a latent or repressed state. The appearance of an actual cancer thus may require activation of a latent virus. Viral carcinogenesis may be a rare event requiring several simultaneous or sequential events.

Multiple factors in virus-induced cancer are demonstrated in the experiments of Henry Kaplan and his group at Stanford University, who showed that leukemia in mice could be evoked by X-ray only if the animals were carriers of a leukemia virus. Thus, in effect, the role of X-rays in this instance was to exteriorize or activate a viral agent already present in the animal. Robert Huebner of the National Cancer Institute also found that a latent cancer virus can be "turned on" by infection by another virus, or a chemical carcinogen.

A practical problem that has become of great importance with the resurgence of interest in viruses and cancer is whether cancer is infectious. Can cancer be caught from patients with cancer, or from household pets with cancer? Is it dangerous to eat chickens or other meat that may contain oncogenic viruses?

At least some human cancers eventually will be found to be produced by viruses, and this implies transmission. Such discoveries may allow us to prevent the occurrence of such cancers by the development of appropriate vaccines. But we still can be confident, on the basis of present knowledge, that no human cancer is communicable; that is, there is no evidence that a patient with cancer can transmit his disease to another person by contact or other direct means of infection. Transmission of cancer between animals and man seems even less likely. How specific and limited we must be when we discuss cancer is immediately evident by the exceptions that are already known. In dogs, there does exist a cancer entity known as venereal sarcoma that is transmitted by direct contact. In chickens, the virus complex that causes several forms of leukemia and other cancers is communicable from infected to young non-infected fowl.

Whether these and similar situations have their analogues in human populations remains to be established by future research.

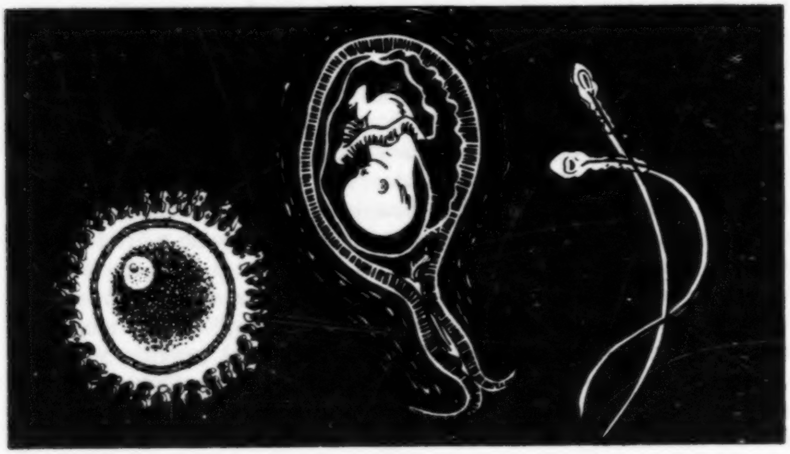
11. "In the beginning . . . ."

A diversion into the meaning of "cause"

In the last three chapters we have concerned ourselves with three major classes of external stimuli that have been defined as carcinogenic. The definition of carcinogenic activity is based on the establishment of a relationship between exposure and an eventual appearance of a tumor. Are such relationships causal? This question requires the examination of what we mean by cause.

Reference to an unabridged dictionary reveals how difficult it is to define "cause" and how many diverse meanings have been given to the word since the days of Aristotle.

The human mind is first confronted with the effect and not with the cause. It is only after the effect is defined that the reasons for (or, more correctly, events preceding) the effect are sought. The relationship between the two is then clarified through an analysis of the intermediate steps, usually referred to as the "mechanism of action" or, for disease, "pathogenesis."



There are few, if any, simple causes in biology. There are, instead, complex situations and environments in which the probability of certain events is increased. The appearance of cancer following exposure to a chemical agent or a surgical procedure merely means that the incidence of this type of cancer has been increased over the incidence that would have occurred without the interference. The increase over the "background noise" must be statistically significant and repeatable. The difference between an "induced" or a "spontaneous" tumor is that with the latter no conscious procedure is undertaken, so that it is of unknown etiology. In neither situation is knowledge implied of the "direct" or "indirect" mechanisms that are involved.

Nevertheless, in specific medical situations we have evolved sets of facts, or evidence, which have to be fulfilled before we accept that a cause-effect relationship has been demonstrated. An excellent example is available in bacterial diseases. Robert Koch, the great German bacteriologist of the last century, described these steps so well that they became known as Koch's postulates. The postulates state that in order to show that a specific microorganism causes a specific disease, we must: find and recover the microorganism regularly from cases of the disease; grow the organism on an artificial medium as a pure culture; reproduce the disease regularly in healthy individuals who are given the pure culture of the microorganism; and again isolate the same microorganism from the individuals who develop the disease under experimental conditions.

These rules of evidence have been most useful in bacterial diseases, but they are not entirely applicable to diseases evoked by nonreproducing agents such as chemicals. With chemicals, the practical acceptance of a causative role is usually based on the regular observation of a specific reaction following exposure of individuals to the chemical, the study of the chemical and the reaction it produces under controlled laboratory conditions, and the ability to prevent the occurrence of the reaction by withdrawing the chemical or protecting the individual from exposure to it.

If this limited, practical definition of cause is made, we know the causes of many specific cancers. For example, the exposure of dye workers to 2-naphthylamine will lead to the appearance of cancer of the urinary bladder many years later. We can prevent the occurrence of these cancers by eliminating 2-naphthylamine and related chemicals from the environment of dye workers. We can also reproduce the sequence of events in dogs and in rabbits. We can thus accept that 2-naphthylamine causes bladder cancer. This statement does not imply, however, that we know the "mechanism," or the steps between the initial stimulus of the chemical and the eventual reaction of bladder cancer. This statement also does not imply that all cancers of the urinary bladder are due to exposure to 2-naphthylamine or related chemicals.

These exceptions or limitations apply just as well to bacterial diseases. In pneumococcus pneumonia, for example, the reaction of the lung to the microorganism that eventuates in a disease called pneumonia is almost as incompletely understood as the transformation of normal cells to cancer cells. And, as in the case of our bladder cancer example, not all pneumonias are caused by pneumococci. Very similar disease processes can be evoked by a wide variety of bacterial and fungal agents, and by chemicals as well.

The reaction of an organism to a stimulus is the property of the organism and not of the stimulus. Obviously, a chemical composed of carbon and hydrogen in a polycyclic structure becomes a "carcinogenic hydrocarbon" because it evokes a cancer response in some organism. The biological effect of an agent is also defined by how man uses it. Thus, a chemical used clinically against a disease is called a drug. The same chemical may be used against insects, and be called an insecticide. The same chemical also may be considered beneficial or poisonous, depending on how it is used.

In order to produce a cancer response, the chemical, or the virus, or the quantum of physical energy, must gain access into the reactive site of the organism. This site of action in cancer must be within body cells. The agent thus must gain access to the cell, and produce a permanent change in the cell that is transmitted to the progeny of the cell. Furthermore, in order that the cancer be recognized, the cellular change must progress through division and growth until a large population of cells is formed.

No tissue is composed of one type of cell, and cells of the same type vary in age and in their relations to each other and to the environment, as well as in such presumably basic characteristics as the number of chromosomes. A completely uniform response of cells or tissues is, therefore, a biological impossibility. Despite the wide variations in individual responses, however, specific neoplastic reactions of organisms of specific strains and species are surprisingly reproducible. This indicates that the reactions are mediated through rather specific biologic, biochemical mosaics.

The probability of a neoplastic event following exposure of an organism to a carcinogenic stimulus is modified by a large series of factors. In regard to the stimulus, among the more evident influences are those of dose, route of exposure, physical state of the material, and length and schedule of exposure. In regard to the host, the probability of the neoplastic reaction is influenced by the genetic background, age, sex, nutritional status, and intercurrent infections. The longer the period between initial exposure and the endpoint of the reaction, the more opportunities occur for the introduction of additional modifying factors. Some of these factors may appear quite subtle. Physiologic processes are influenced by sociologic and psychologic factors. Some influence of sociologic and psychologic factors upon the occurrence and growth of cancer therefore should occasion no surprise; the degree of their importance is another question.

The chain of events that must transpire in the initiation and growth of cancer is long. The factors that may influence this process are many. Many points therefore exist at which the process can be entered and interrupted for preventive or therapeutic effects.

12. Cells and organisms

A complex community

The basic biological unit of plant and animal life is the cell. All higher animals that multiply by sexual reproduction begin with the union of the male and female sex cells, which are specialized cell units containing only half of the genetic material characteristic of the species. The resultant divisions of this union eventually form the whole organism.

The original few cell divisions following fertilization are symmetrical, but if this continued, we would be monotonous spheres. Soon the cells orient themselves along a longitudinal plane and the mass begins to assume increasingly different shapes at various points. This is the phase of differentiation, in which from the originally identical cell units there arise the different tissues and organs of the body. Eventually, from the original fertilized egg there develops a complex, closely integrated community of some 100 billion cells that comprise the adult human body. Each one of these cells has the genetic identity of that individual, yet the cells can be as different as those that make up the brain, the liver and the skin. Some tissue cells

continue to divide at relatively constant rates throughout the life of the individual, replacing the worn out cells and thus maintaining a dynamic equilibrium. This is the case for the skin, which is continually replaced from the deeper layer. Other tissues, such as the liver, have the power to replace cells following injury or removal of part of the organ. Still other cells, among them those of the central nervous system, are so specialized that they lose their property of being able to replace themselves by division.

As important as the process of differentiation, which converts a round ball of a few dozen cells into mice, whales or human beings, is the process of regeneration or healing. When a tissue is injured so that some of the cells are destroyed, ordinarily the remaining cells divide to bridge and repair the damage. If this damage is too great, or if it involves cells that are unable to divide, the special connective tissue cells complete the repair by forming scar tissue. In both the process of differentiation and of healing, the remarkable feature is that the cells "know" when to stop dividing.

Differentiation and regeneration, as all other biologic processes, involve both heredity and environment. Hans Spemann, in his classic work on experimental embryology, showed that undifferentiated cells from the limb-bud of embryos would form limbs when they were transplanted to other parts of the embryo. These cells, in more modern terminology, were genetically programmed to form limbs. On the other hand, when urinary bladder epithelium is transplanted under the skin in dogs, typical bone is formed. The new environment thus exteriorized the potential of the bladder cells to develop bone.

A technique which has been most useful in the study of cells is known as tissue culture, first introduced by Ross Harrison of Yale in 1907. A small fragment of tissue, usually from an embryo, is placed in blood plasma, and maintained under sterile conditions in a small flask in moist, warm conditions. The cells from the tissue will continue to grow and to divide, and can be observed under the microscope and photographed. Under optimum conditions certain tissues may continue to multiply indefinitely. Alexis Carrel of France, a good showman as well as a Nobel prizewinning scientist, celebrated for many years the birthdays of such a tissue, first derived from the heart of an embryo chick. He would point out that were the cells able to divide without limitation, their mass would have exceeded that of the earth.

It is this built-in limitation of growth, the acquisition and maintenance of function, the dynamic equilibrium between various parts and organs, in other words, the planned discipline of an integrated complex colony of cells of the individual that distinguishes normal growth and cancer.

Cancers of all kinds are tissues, too. They are composed of cells, as can be observed under the microscope. Many of the cells are somewhat larger and abnormal in shape, but even more resemble the normal organ tissue from which they arose and by which they can be identified. Some cancers form glands and secrete the same materials as the glands they mimic. But the restraint of growth is missing, and instead of stopping their reproduction at the appropriate boundary, the cells continue to divide, invade and behave in a manner that is not compatible with the integrated behavior demanded of normal tissue. Cancer growth is not necessarily more rapid than normal growth. In fact, many normal growth processes exceed those of most cancers. Among these are embryonic growth, which develops from one cell to a 7-pound baby in 9 months. But the baby is then ready to emerge into the world, to continue its well-regulated growth; for cancer there is no such endpoint.

Cancer cells, too, can be grown in tissue culture. In this environment also the division rate of cancers is often no more rapid than that of connective tissue cells. But their lack of integrated behavior is again evident. Normal connective tissue cells grow in smooth, one-cell-thick layers on surfaces provided for them, producing netlike structures; when a cell encounters another cell, further division is inhibited or proceeds in another direction. But cancer cells tend to grow in clumps, and the proximity of their neighbors does not inhibit them. Instead, they climb on each other, and as a consequence choke off some of their kind from the food and oxygen supply.

That cancer is a process affecting the cell is further shown by experiments involving the transplantation of cancers from one animal to another. This was first performed successfully in dogs by a Russian veterinarian, M. Novinsky, in 1876. When inbred animals became available, the transplantation of cancers from one animal to another of the same genetic constitution could be carried out with uniform success. Small bits of sterile cancer tissue are taken from a mouse or a rat and injected under the skin of another mouse or rat of the same strain. After a short time, the cancer starts growing in its new location, by the multiplication of the cells that comprise it, and so on through a whole series of animals. Some transplantable tumors have been maintained in this manner since the early years of this century, and are known by the names of their original discoverers. This continuity of the tumor with maintenance of its appearance and behavior through many generations indicates that the cellular change involves a permanent change in either the genetic mechanism of the cell, or some transmissible, reproducible material within the cell. Transplantation requires living, reproducing cells. If a tumor appears at the site of inoculation of presumably killed or filtered tumor tissue, this is presumptive evidence that a subcellular or viral agent is involved. This would not be transplantation, but the induction of a new tumor from the tissues of the host animal.

In 1936 Jacob Furth of New York took another step in the demonstration of cancer as a disease of the cell by transplanting leukemia from one mouse to another with single cells. And in 1943, Wilton Earle and his associates at the National Cancer Institute published their meticulous studies on the conversion of normal cells to cancers in tissue culture. Whatever the mechanism of this conversion, it was again shown that it occurs at the level of the cell, without the need of the whole organism and its many reactions, and that this conversion is a permanent one transmissible to the progeny of the cell.

13. Within the cell

The new biological frontier

Molecular biology is a science born of this century. It concerns itself with the structure, synthesis and function of living matter at the molecular level. Its findings are relevant to cancer, virus diseases, metabolic disorders, congenital malformations and hereditary defects. Eventually molecular biology will allow man to manipulate genetic characteristics of his own and other species. The effects will be as profound and as far-reaching as the effects of atomic power and of space exploration.

An early milepost in molecular biology was the work of O.T. Avery and two young associates at the Rockefeller Institute in New York. In 1944 they reported that pneumococci of one type could be transformed permanently to another type if they were grown in media containing nucleic acids from the latter type. The observations pointed to nucleic acids, rather than proteins, as chemical carriers of

genetic information.

In 1953 J. D. Watson and F. H. Crick announced the double-helix structure of deoxyribonucleic acid, the chief building block of living matter. Subsequent discoveries followed at a dizzying pace. As one measure of pinnacles of biomedical research, the majority of subsequent Nobel prizes in medicine was claimed by workers in molecular biology.

The facts of cellular structure and function apply to the whole world of life, from bacteria to man. It is, in biochemical terms, the confirmation of Darwin's revelation of the evolutionary continuum of all living things.

The cell is composed of a darkly staining, compact nucleus, a liquid cytoplasm around the nucleus containing mitochondria, ribosomes and less organized particles, and the cell membrane enclosing the structures. The nucleus contains chromosomes, discrete strands that carry the genetic orders that determine the structure and function of the cell and its daughter descendants.

In man, there are 46 paired chromosomes, a fact established only in 1956. Until then, due to an old error of observation, it was taught that man possessed 48 chromosomes. With modern techniques of tissue culture, squash preparation of the cells, and the stopping of cell division at a point when the chromosomes separate by the use of a drug called colchicine, a whole series of important observations became possible. One pair of the chromosomes determines the sex of the individual: an XX pair resulting in a female, and an XY pair resulting in a male. The sex chromosomes look different, and the sex of a person can be determined by looking at his individual cells. Sometimes an extra sex chromosome is found, and such persons may be sterile and show other sex abnormalities. A very specific chromosome abnormality is always seen in a mental deficiency called mongolism, now renamed Down's syndrome. In one form of cancer, chronic granulocytic leukemia, there is often a specific chromosomal abnormality, the so-called Philadelphia chromosome.

The chromosomes consist of tightly coiled double strands of a molecule that has an external backbone of sugars and internally interlinked, in a zipper-like fashion, a series of nucleic acid components. These molecules, with molecular weights of several million, are called deoxyribonucleic acid, or DNA for short. They govern not only the genetic continuity of the species, but all the essential processes of the life of the cell. The arrangement of the four nucleic acid components along the DNA molecules determines these operations in a manner analogous to the instructional tapes of the computers. For the reproduction of the cell by division, the DNA strand unzippers itself into 2 halves, and from the raw nucleic acid building blocks and other components in the cell, constructs an exact copy of the half-strand, and then segregates the identical chromosomes for the mitotic phase of division.

The chromosomal DNA is also the manager for the daily life functions of the cells, which it guides through two other key chemicals. One is *RNA*, much smaller, single strand molecules of nucleic acid arranged along a more soluble form of the sugar, ribose. The other is *proteins.* The RNA molecules are formed in the nucleus according to the blueprint of the DNA, and these messengers proceed into cytoplasm to attach themselves to the ribosomes. There other RNA molecules convey the amino acids for assemblage into the operational proteins such as enzymes.

In 1973, Stanley N. Cohen and a team of Stanford and University of California scientists reported the successful recombination of DNA. This was a culmination of discoveries on breaking and rejoining DNA molecules; of gene carriers that can replicate and be linked with DNA segments; of introducing DNA into foreign cells; and of selection of clones of resultant molecular chimeras.

The practical and theoretical implications of recombinant DNA made it a topic of international interest and concern. Recombinant DNA is a powerful tool in studies on mechanisms that control gene functions, and, as such, in cancer research.

In multicellular organisms, cells of different tissues undertake specialized functions, through the process of differentiation. Differentiation is a loss of the ability of cells to manufacture all but a set of enzymes specified for their function. This loss is thought to be achieved by having some sites on the genes in the chromosomes covered up or inactivated. The process can be reversed by demand, such as the appearance of "induced" enzymes in the liver that is confronted by some toxic chemicals. Reversal is also evident in the change to cancer, when enzymes typical of embryonic but not of adult tissues reappear in the tumor cells.

In order to exist, the cells of the body must obtain oxygen for their respiratory functions, a whole series of nutrients as sources of energy, and amino acids, vitamins and other essential chemicals that they cannot manufacture themselves for the building blocks to replace and substitute wornout or lost portions of their structure. The body and all its component parts are in a constant, active state of dynamic equilibrium. One of the great contributions of the use of stable and radioactive isotopes as tracers of biological reactions was the demonstration that there are no "fixed" tissues, that all tissues and cells of the body constantly replace themselves in part, substituting new molecules for old.

In the dynamic state of biological life, the myriad of chemical reactions must occur within a limited range of temperature, yet they must occur rapidly and smoothly. Even such a relatively simple event as the transfer of oxygen through a membrane between the air sac of the lung and the blood would take too long at the body temperature of 38°C. All such reactions or transfers, splitting into component parts, and the synthesis of new complexes are mediated through the action of specialized proteins called enzymes. The enzymes are manufactured from amino acids by the RNA on instructions from the genic DNA of the cell, and go forth to regulate the life chemical processes in the cells or at sites distant from the cells.

A mammalian cell contains an estimated 100,000 different enzymes to perform up to 2,000 chemical reactions. Ten or more different enzymes may be needed to convert one chemical to another. Several hundred enzymes, from aldose to zymohexase, have been identified. Many have been isolated and crystallized, and some have been synthesized from amino acids.

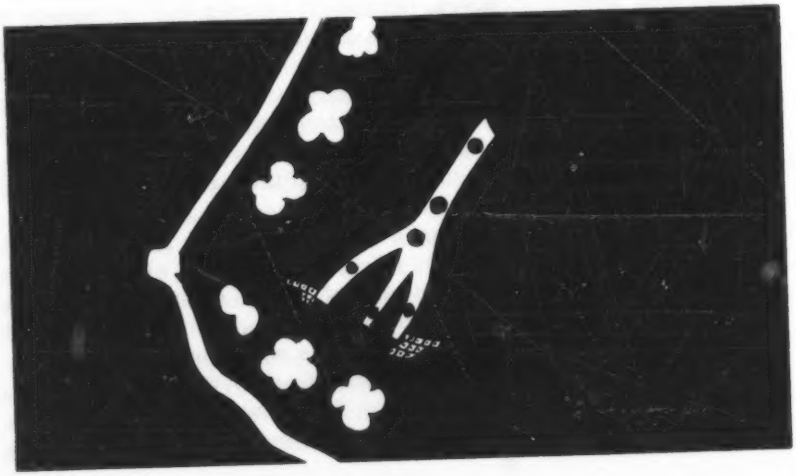
Vitamins form a part of certain enzymes, but the body cannot synthesize these parts of these enzymes and must obtain them from its environment. Closely allied in activity to enzymes are chemical cell products called hormones, which also regulate at a distance many of the metabolic and endocrine functions of the body. The pituitary protein hormones act as the thermostat in the coordination of another large species of steroid hormones. As has been demonstrated recently, pituitary hormones are in turn regulated by chemical signals from the brain.

14. The crab emerges

The birth and the behavior of cancer

Even four decades ago, there was widespread scientific agreement that the production of cancer could be explained by one of two biological processes. One was called "somatic mutation," proposing a genetic change in the body cells as the basic mechanism; the other was the invasion of the cell by a virus, endowing the infected cells with cancer properties. Essentially the same choice between the two hypotheses confronts us today, but we can now begin to consider with some intelligence the molecular level of the reaction, and to conceptualize a reasonable reconciliation of these two seemingly divergent viewpoints. Even more important, we can now test many of our hypotheses with actual experiments, using the ever-improving tools of electron microscopy, X-ray diffraction, immunochemistry, electrophoresis and other exact physicochemical methods of separation of complex molecules.

We must account for the basic characteristics of fully developed



cancer, with its anaplasia and autonomy, passed on from generation to generation of cells. Some permanent change seemingly must occur in the DNA molecules that compose the genic directorate of the cell. The discovery that nucleic acids from the Shope virus become incorporated in the DNA structure of the nucleus of the invaded cell offers a reasonable model for the carcinogenic action of DNA viruses. The model did not seem to fit oncornaviruses, since RNA was not supposed to produce DNA. In 1970, however, Howard Temin of Wisconsin and David Baltimore of the Massachusetts Institute of Technology discovered that RNA viruses contained an enzyme that could manufacture DNA, the "reverse transcriptase." It is now possible to visualize both DNA and RNA viruses becoming parts of genetic matter of chromosomes. There they exist in a "repressed" or latent state. When they are activated, they endow the cell with its neoplastic characteristics, including continuation of neoplastic identity during subsequent divisions.

Only further investigations will establish whether simpler chemicals, such as the carcinogenic hydrocarbons, can act directly on the cellular DNA, or whether they activate some virus-like entity already present in the cell.

It is probably simplistic to try to explain all transformations of cells to cancer by one mechanism, or to attribute the same mode of action to all chemicals, viruses, and physical agents that evoke cancer. Many chemical carcinogens produce mutations in bacteria and in fruit flies, but there are exceptions. Although the mutation concept is attractive, epigenetic alternatives do exist. It is also not clear whether one mutation or more are necessary in the cell-cancer transformation.

Neoplastic growths can occur in any tissue of the body capable of cell division, and represent a wide spectrum of appearance and behavior. There are benign hyperplastic masses that regress, benign tumors that remain localized, dependent cancers that grow only if certain hormonal or other host conditions are met, invasive and metastasizing cancers, and finally the rapidly aggressive neoplastic cancers. These are not necessarily progressive stages of neoplastic growth, but may represent different terminal changes. Tumors do tend to become more malignant on serial transplantation in animals, but this may be due to selective survival of the more rapidly growing cells rather than to further cellular alteration.

Stimuli that convert normal cells to cancer cells are not limited to an individual cell, but must affect a population of cells. In an investigation of the globulin patterns of tumors arising from plasma cells, the myelomas, it was found that the tumors showed individual globulin patterns, rather than containing a wide variety of such patterns, which suggested single cell points of origin. On the other hand, analysis of the origin of skin cancers following ultraviolet radiation leads to the conclusion that the simultaneous stimulation of a large number of cells is involved. It is likely that both situations hold in different circumstances. Under the specialized conditions of tissue culture, several lines of sarcomas have been established from cell populations that were started from single connective tissue cells.

Cancer cells grown in flasks, as tissue culture, behave differently from normal cells. Normal cells stop dividing when they come in contact with other cells, as a recognition of their appropriate territory. Cancer cells continue to divide and to pile up on top of each other, having lost the property of contact inhibition. Normal cells under tissue culture conditions undergo a limited number of divisions. Cancer cells escape this limitation, and appear to be able to propagate indefinitely.

There are no characteristics of appearance or biochemistry that distinguish all cancers from all normal tissues. However, when specific cancers are compared with the tissue from which they arose, many differences are detected. Unfortunately, the meaning of these differences is obscure. Cancer cells tend to be larger than normal cells; the nucleus particularly is enlarged and contains more haematoxylin- or Feulgen-staining material. As a consequence, the nuclear-cytoplasmic ratio is often larger than that of comparable normal cells. A greater proportion of the cells at any given time appear to be in normal or abnormal mitosis. The nucleolus is usually more prominent in cancer cells, and rather often more than one nucleolus is observed. Increased numbers of chromosomes, and abnormal chromosomes are often seen in cancer.

Biochemically, one of the characteristics of many cancer cells was discovered by Otto Warburg of Berlin over 40 years ago. This is the way that cancer cells utilize glycogen as a source of energy. In almost all normal cells (and, as usual, there are a few vexing exceptions), glycogen is broken down to water and carbon dioxide through a series of steps if the cells have an adequate supply of oxygen. This is known as aerobic glycolysis. If normal cells are deprived of oxygen, the process of sugar breakdown stops at an earlier stage, of lactic acid; this is known as anaerobic glycolysis. Cancer cells, in general, often display anaerobic glycolysis even when adequate oxygen is available, and this may be attributable to abnormalities in enzymes such as phosphohexose isomerase. As a consequence of this incomplete breakdown of glycogen, cancers form and accumulate an excess of lactic acid. When a rat with a transplantable cancer is given a large amount of glucose, there is a drop in the pH of the tumor because of the increase of lactic acid. An extension of these observations is the finding of increased lactic dehydrogenase in cancer tissue and in the blood of some animals and patients with cancer.

From the earliest descriptions of cancers under the microscope, starting about 1830, pathologists noted that cancers resembled embryonic tissues. This resemblance was most striking in the rapidly growing cancers. There was a rough relationship between malignancy and dedifferentiation from the adult toward the embryonic state. In 1963, a Russian investigator, G. Abelev, found that liver tumors in mice contained a protein that was present in embryonic liver but not in adult liver. Patients with liver cancer also had this fetal protein in their blood. This was a biochemical demonstration of dedifferentiation. Genetic information repressed in adult tissue reappeared in a cancer arising from the tissue. Phil Gold of Canada in 1965 reported the appearance of carcinoembryonic antigen in patients with cancer of the colon. The procedure has become a useful test for monitoring patients treated for colorectal cancer.

Cancer as a disease is manifested not by single cells but by a large population of such cells and their interaction with the normal processes of the host. The cocarcinogenesis work of Berenblum, for example, suggests that individual cells possessing the potentials of cancer may lie dormant for protracted periods. And, although leukemia has been transplanted successfully in mice by the use of single cells, usually a dose of several thousand cells is required for the passage of tumors from one genetically identical animal to another. Thus, cancer as an entity starts as a colony of cancer cells, with the resultant development of interplay of factors between the individual cells of the colony, and the reactions between the cancer colony and the host in which the colony exists.

In order to survive and to grow, the cancer must derive a nutrient supply from the host. For most solid tumors, this requires the acquisition of a blood supply. Observations on the larger blood vessels of tumors, by means of X-rays and radio-opaque media, indicate that such vessels are increased in number and tortuosity and many even form patterns that are helpful in the localization of the mass. However, microtechnique studies on skin tissues indicate that the increased blood supply does not represent better oxygenation and nutrition, for the blood flow is stagnant.

The cells of cancers arising from epithelial tissues are, in general, less cohesive than the normal epithelium. Cancer cells tend to contain less calcium than normal cells, and the cell membrane has fewer glycoproteins. Under the electron microscope, the intricate joints between normal epithelial cells become less evident and are replaced by extension of the cells beyond their normal boundary, or microinvasion.

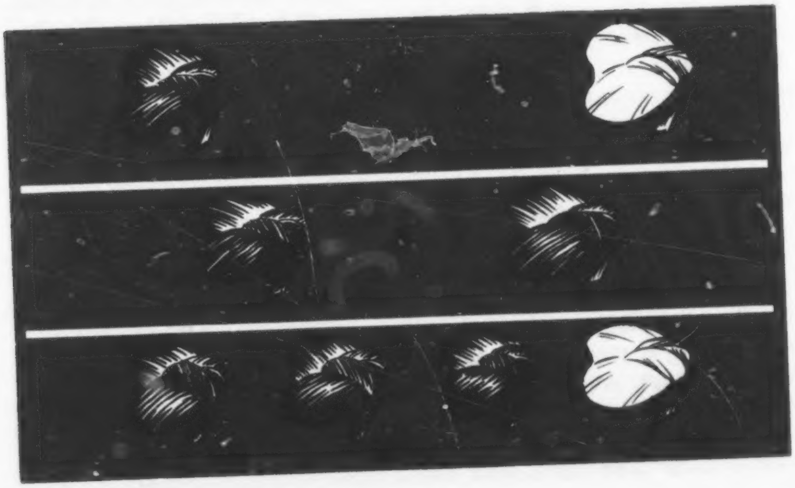
Many cancer cells are motile, as are normal cells under tissue culture conditions. With some transplanted tumors, cancer cells can be isolated from the liver of the animal within hours after the implantation of the tumor under the skin. Such individual or very small clumps of cells are destroyed, since they do not give rise to metastatic masses. Cancer cells sometimes can be identified in the blood and other tissue fluids of patients with cancer. No clear relationship is demonstrable, however, between recurrence or metastasis of cancer and detection of cancer cells in the blood. This is attributable to at least three factors, the first one being that there is considerable error in the identification of such cells as cancer. The second is that even correct morphological identification does not mean that such cells are alive in the sense of being able to reproduce. The third is that most individual cancer cells are destroyed before they can lodge in a capillary, attach themselves to the blood vessel wall, and penetrate into the deeper tissue where they can divide and set up a new colony, a metastasis.

The biological hub

The question, "Is it heredity or environment?" is now seldom heard, because it is really not very meaningful. The effects of any environmental stimulus on an organism are modified by the inherited traits of the organism, and the inherited traits and capabilities of an organism can be modified by the external or internal environment.

Cancer research began in earnest at the turn of this century, and its first materials were the breast cancers in small laboratory rodents. It was noted that cancers occurred more frequently in certain families of such animals, and it was postulated that such familial aggregation involved genetic factors. For the resolution of these factors, genetically defined animals were necessary, and these were developed by brother-to-sister selective breeding.

This task was undertaken by geneticists, notably Sewall Wright of Chicago, Clarence C. Little and Leonell C. Strong of the Jackson Memorial Laboratory in Maine. Dozens of strains or families of mice and guinea pigs were derived, the animals being as identical as twins and having predictable frequencies of certain types of cancer. For



example, the strain A albino mouse develops primary lung tumors and, among breeding females, breast cancers. The strain C3H is noted for its early development of breast cancer in females, and of liver tumors in the males. Other strains, such as the C57 black, are useful because they have been selected for low occurrence of tumors. Yet other strains have been developed for characteristics that mark certain genes, enabling studies on the relationship of such features to the development of cancer.

A long series of investigations using inbred strains led to the conclusion that cancer was not a single genetic characteristic, and that different mosaics of genetic factors were involved in the susceptibility to different cancers. Strains of mice that developed lung tumors, for example, could be relatively resistant to liver tumors. In general, if a high-cancer strain was crossed with a low-cancer strain, the hybrids showed an intermediate susceptibility to cancer. There were some exceptions, but in general the frequency of cancer in the hybrid cannot be predicted by knowing the frequency of the occurrence in the parent strains. Studies on breast cancer in mice revealed the presence of an extrachromosomal factor that led to the discovery of the Bittner virus. The genetic background modifies susceptibility to the virus and remains of importance. In some strains of mice that develop but few breast cancers, the introduction of the Bittner virus converts the strain to a high-cancer line in subsequent generations. In others, the incidence of breast cancer drops sharply after a few generations, as the virus disappears. Here the genetic constitution of the animals overcomes the carcinogenic virus and its manifestations.

The mosaic of hereditary factors thus participates in every step of the cancer process: at the reaction to the carcinogenic compound or virus, to the tissue susceptibility to the neoplastic transformation, and to the subsequent growth and metastasis of the cancer. The immune mechanisms that are involved in the acceptance or rejection of tissues are also dependent upon the genetic constitution of the organism.

In animal species whose breeding patterns man wishes to manipulate, it is possible to segregate and develop lines of high frequency of specific cancers, as was done in mice. It is also possible to reduce cancer occurrence by selective breeding techniques. For example, the problem of cancer of the skin around the eyes of white-faced Hereford cattle that are exposed to high levels of solar radiation could be reduced or eliminated by introducing more protective skin color. As in all purposeful genetic choices, however, such a change may be associated with many other unpredicted and even less desirable new characteristics. As another example the occurrence of liver cancer in trout is most evident in the rainbow species, and much less so in other trout varieties. This neoplasm could be reduced by crossbreeding rainbow trout with other trout, but a better approach is

SOME HEREDITARY CANCERS OF MAN

I. Hereditary neoplasms
    1. Retinoblastoma
    2. Multiple polyps of colon
    3. Gardner's syndrome
    4. Chemodectoma
    5. Pheochromocytoma and thyroid cancer
II. Preneoplastic states
    1. Nodularity syndromes
        e.g. Neurofibromatosis
        Tuberous sclerosis
    2. Genetic skin disorders
        e.g. Xeroderma pigmentosum
        Albinism
    3. Chromosome breakage disorders
        e.g. Down's syndrome
        Bloom's syndrome
        Fanconi's syndrome
    4. Immune deficiency syndromes
        e.g. Ataxia telangiectasea
        Agammaglobulinemia

to avoid contamination of the food by mold that produces the carcinogenic aflatoxins.

Until 1960, scientists believed that only germ cells (eggs and sperm) were capable of fusing and forming reproducing cells. Then G. Barski and his colleagues in Paris found that body cells grown in tissue culture also could unite and form hybrids capable of reproduction. Such hybrids can now be produced between cells from different species, such as mouse and man. This remarkable technique of somatic cell hybridization has speeded analysis of chromosome mapping of normal and neoplastic cells, and of the relationships of such geography with function. It is now also possible to create animals with four parents, by removing fertilized ova after a few divisions, fusing them, and transplanting the tetraparental mass into the uterus of still another female. This is another technique that is contributing to our knowledge in genetics and other biological sciences.

In human populations, most of the common forms of cancer do not show obvious familial aggregations. Special studies, however, do reveal relatively minor degrees of such aggregation in cancer of the breast, rectum and lung. Familial aggregation of a characteristic does not in itself indicate a hereditary factor, since families also share common environmental situations. The hybrid nature of the human species makes exact genetic studies difficult. Some clarification of the relative roles of heredity and environment is afforded through registries of identical and fraternal twins. If one identical twin develops leukemia, it is a 1 in 6 chance that the other twin will also develop leukemia, usually within a year.

There are some cancers and precancerous conditions in man that are primarily determined by the heredity of the individual. Retinoblastoma, a tragic cause of blindness and death in children, is inherited as a dominant trait, and the presence of this trait has been suggested as a valid reason for eugenic sterilization of the parent so afflicted. An abnormal sensitivity of the skin to ultraviolet radiation, called xeroderma pigmentosum, almost inevitably develops into cancer, and is a hereditary disease. So is the familial multiple polyposis of the colon, which develops into cancer during the second and third decade of life. Some of the hereditary cancers and precancerous states are listed in the table on page 77.

It should be pointed out that the occurrence of skin cancer in man has a strong hereditary factor, in that the characteristic of dark skin protects the individual against the carcinogenic effects of ultraviolet radiation.

As a practical point of advice to relatives of patients with cancer, we now should avoid a blanket statement that cancer is not inherited. For most specific cancers, it is better to say that the risk of developing such a cancer by the relatives is no greater than that of the general population. But the daughters and sisters of women with breast cancer, and the children of patients with rectal cancer should be informed of their increased risk, genetic or otherwise, which makes desirable closer medical surveillance.

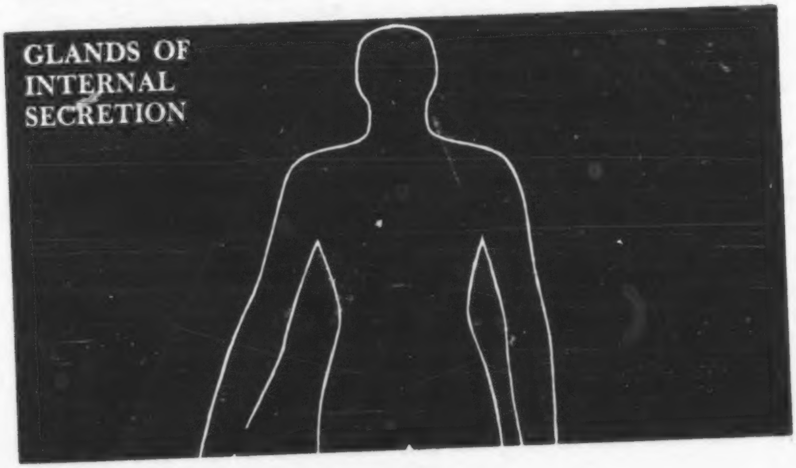
The study of genetic traits and their association with cancer and other diseases in human family units is a fertile and important field for research.

16. Hormones

Internal regulators of growth

One of the most interesting and best studied areas of biological research is endocrinology. It concerns the glands of internal secretion, which produce chemicals that are important in the growth and regulation of many functions of the body. The anterior pituitary gland, from its position at the base of the brain, is the conductor of this orchestra; perhaps a better or an alternative metaphor is one of a thermostat. At any rate, an intimate relationship exists between the pituitary and the thyroid, the adrenals, and the ovary and testis: when the action of the latter glands is inadequate, the pituitary puts out increased amounts of stimulating protein substances known as the trophic hormones.

Abnormally deficient or excessive hormone production leads to some of the more bizarre clinical manifestations, and these have attracted medical interest since antiquity. During the 1930's, the first pure hormones were isolated and chemically characterized, and there



became available an extensive number of chemicals with remarkable physiological activity. The female sex hormones, estrogens and progesterones; the male sex hormones, androgens; the adrenal corticoids are the chief examples of steroid chemicals. Thyroxin and parathormone, pitressin and the anterior pituitary hormones are examples of nonsteroid chemicals.

The relationship of hormones to cancer was one of the earliest areas of interest in cancer research. Leo Loeb of St. Louis, Mo., demonstrated by 1918 that breast cancers could be prevented in female mice if the ovaries were removed. Furthermore, breast cancers could be induced in male mice, which do not develop breast cancer, if they were castrated and had ovaries implanted under the skin. With the advent of pure estrogenic compounds, A. Lacassagne of France in 1932 reported that these also would evoke breast cancers in males of susceptible strains. It was shown subsequently that breast cancer in mice required the presence of three complexes: genetic susceptibility, the hormonal status, and the milk-transmitted Bittner virus.

Large doses of estrogen, given over protracted periods, will also lead to the development of testicular tumors of the interstitial cell type, cancers of the uterus, pituitary tumors and leukemia in specific strains of mice. William Gardner of Yale attributed these effects to the producton of a hormonal imbalance, which could be achieved by several procedures other than exogenously administered hormones. The appearance of cancers and other tumors of the adrenal cortex was reported following castration, an effect that could be prevented by the administration of estrogens. Ovarian tumors were produced in rats following the transplantation of the ovaries to the spleen. In this location, the ovarian hormones were secreted into the blood supply to the liver, where they are inactivated. The pituitary was thus stimulated to produce increased amounts of gonadotrophic hormones that forced the ovaries in the spleen into increased activity. The tumor reaction also could be prevented by injections of estrogen, or by leaving one of the ovaries in its normal position.

More increased activity, however, is not a carcinogenic precursor, and other factors are undoubtedly operative. The lactating breast, for example, represents the most active hyperplastic phase of the tissue, yet is not especially susceptible to becoming cancerous. Cancers appear to arise more readily during regressive phases when small islands of active tissue remain in an otherwise somewhat atrophic organ. On the other hand, mice that develop testicular tumors manifest an increased resistance to estrogens that allows them to protect the sperm-producing elements of the testis much better than mice of strains that respond to estrogens by a severe early atrophy of the testis. It is probable that in many of the cancers evoked by estrogens, the reaction is mediated through the pituitary. These interrelationships may involve not only other endocrines, but detoxification of steroids by the liver, folic acid metabolism and nutritional factors. The complex situation is well illustrated by Howard Andervont's findings at the National Cancer Institute, that the incidence and age of occurrence of breast cancer in mice are affected by the number of animals that are kept in one cage. The interpretation here is that a single mouse in a cage has an unlimited access to the food supply, but is deprived of the warmth achieved by communal nesting. These factors affect the estrous cycles of the animals, which are related to hormone levels and, thus, to the development of breast cancer.

In some strains of mice, the occurrence of leukemia can be increased by injections of estrogens. This reaction probably involves the adrenal cortical hormones, which affect the lymphoid tissues. The hormonal status of the animal also affects other neoplastic reactions. The production of liver cancer with azo dyes in the rat is markedly inhibited by the removal of the pituitary gland. It has been shown recently that hypophysectomy also prevents the development of "spontaneous" liver tumors in mice. Hypophysectomy also leads to the inhibition of the formation of subcutaneous sarcomas in mice receiving polycyclic hydrocarbons.

The great use of estrogens and other hormones since their introduction into clinical practice almost 40 years ago has produced no demonstrable increase in the incidence of breast cancer in women or in men. A careful study of the rare breast cancer in males failed to show a greater antecedent history of the use of estrogens and other hormones than matched control patients. Breast cancer in men treated with estrogens for prostatic cancer may have been metastases from the prostate rather than being primary in the breast. However, in 1971 Arthur Herbst and his colleagues in Boston reported the occurrence of cancer of the vagina in some daughters of mothers who had taken diethylstilbestrol (DES) in large doses during their pregnancy. This synthetic estrogen is carcinogenic for the human embryo, with the effect becoming evident 15 years or more later. Estrogens, given for menopausal symptoms, increase the risk to developing cancer of the endometrium, the lining of the uterus.

The role of the pituitary gland in the origin of human cancer is also not clear. The risk of developing cancer among patients with acromegaly, one type of hyperpituitarism, and among pituitary dwarfs, one type of hypopituitarism, was the same as that to be expected in the general population of a comparable age. One report on the effect of thyroid activity and cancer occurrence suggests that cancer is less frequent among patients with hyperthyroidism and more frequent among patients with hypothyroidism than among people with normal thyroid function.

We have touched upon some of the interrelationships between the development of cancer and hormones. There are also some significant effects of hormones on established tumors and their growth. It has been known since 1896 that some premenopausal women with advanced breast cancer had temporary regressions of the cancer following the removal of the ovaries. In prostatic cancer castration also often leads to the regression of the tumor. These two cancers in man, even at the stage when the cancer manifests its ability to metastasize, are still in part "hormone dependent."

Hormone dependency is also observed in some experimental tumors in animals. Breast adenomas of rats, or the interstitial cell tumors of the testes in mice, can grow only if the animal continues to receive estrogen. Some thyroid tumors in rats receiving thiouracil also continue to grow only if the normal thyroid function is kept suppressed.

When mice of a susceptible strain are implanted with estrogen pellets, microscopic tumors of the testis are seen 8 to 12 weeks later; if the pellets are removed at this time, practically no mice develop gross tumors. But if the pellets are reimplanted several months later, the tumors promptly start growing. Many of the large tumors no longer need estrogen for further growth, showing a loss of hormone dependence.

The hormone dependence of some human tumors can be exploited clinically in several ways. Castration for prostatic cancer and breast cancer can be substituted or complemented by the use of large doses of appropriate sex hormones. Alexander Haddow of London showed that diethylstilbestrol and other estrogens also have regressive effects in advanced breast cancer in postmenopausal women. The paradox of presumably opposing hormones having similar end effects is probably resolved by the fact that both hormones in large doses suppress the anterior pituitary gland, and this is the possible mode of action. Support for this is derived from the direct attack on the pituitary. Its removal also produces beneficial effects in many patients with advanced breast cancer.

An interesting feature of some cancers is the elaboration of hormones, which should not be made by the tissue from which cancers arise. This "inappropriate" secretion of materials with hormonal activity may be an attempt of cancer to redifferentiate.

17. The food we eat

Nutrition and cancer

Life depends upon energy and building blocks that are derived from food. The main sources of energy are carbohydrates, such as starches, which are broken down to sugars, and fats, which are converted into fatty acids. Proteins are necessary not only as energy sources but as building blocks that are reconstructed with the amino acids derived from proteins. In addition to these major diet components, called macronutrients, the body requires minerals and salts, and a class of micronutrients called vitamins. These are similar to enzymes, since they are needed in certain essential metabolic reactions, but unlike them cannot be made by the body and have to be supplied from external sources.

Cancer, being a form of cellular growth, requires the same types of nutrients as the normal body. Despite intensive experimentation, no specific nutrient has been found that is essential for the development or growth of cancer and not needed by the host. However, changes in diet that produce effects on the animal, such as severe weight loss, also affect tumor growth. In general, the fully developed

cancer is a very successful competitor for a limited food supply.

One of the more common manifestations of advanced cancer disease is loss of weight, to the extent of wasting, or cachexia. Even when the host has reached this stage, the cancer continues to grow. Years ago scientists observed that by feeding cancer tissue to rats on which similar cancers were growing, this body weight loss could be partly prevented. The cancers, therefore, were competing favorably for the nutrients of the host, and acting as "nitrogen traps" by accumulating nitrogenous compounds needed for body function. Attempts to identify more specific factors that are replaced by feeding tumor tissue, however, have not been successful, but the sodium ion appears to be important.

Nutrition, as a source of energy and of material for the synthesis of new tissue, plays a role not only during the growth phase but also during the development phase of cancers. Albert Tannenbaum of Chicago showed that by the simple expedient of cutting the food intake of mice by one-third, at which level the animals were quite healthy but not as fat, the occurrence of breast cancers was reduced by 50 percent or more. Restriction in the total caloric intake also reduced the occurrence, or slowed the time of appearance of several other types of tumors in mice. Human parallels of the mouse findings were not elicited at that time, and interest dipped in nutritional research in cancer.

After two decades of relative neglect, attention is again being focused upon the role of diet in the development of cancer. A variety of studies in laboratory animals and in human populations suggest that factors such as maintenance of ideal body weight and dietary content of fat and fiber influence cancer incidence.

There seems to be no doubt that diet can and does influence the development of cancer. Further research in identifying the materials and mechanisms that are involved should be rewarding.

The development and growth of certain specific cancers in animals are also modified by the content of vitamins and other micronutrients. The early experiments on the production of liver cancers in rats fed on azo dyes that were reported from Japan could not be duplicated in the United States. Analysis of the discrepancy showed that the Japanese laboratory diet consisted mainly of polished rice, whereas in the United States it was supplemented for more optimal intake. Further studies revealed that riboflavin, one of the B vitamin complex, protected the animals, probably in the detoxification of the azo dyes. The role of these vitamins was not demonstrated in the occurrence of several other experimental tumor models, including the "spontaneous" hepatomas of mice.

There is evidence that vitamin deficiency in man plays a role in the occurrence of cancers of the oral cavity and the esophagus. Chronic vitamin B complex deficiency, due to inadequate supply of vegetables, appears to be incriminated. However, reliable dietary histories over many years are notoriously hard to come by, and such deficiencies are probably a part of a number of necessary factors. Experimentally in animals, and also in human beings, deficiency of vitamin A produces a thickening and piling up of the lining of the stomach and epithelium.

The mouth is one of our major routes of contact with our environment. The food we eat may contain preservatives and other, purposefully introduced additives; chemicals may be altered by heating and other processes; it may become contaminated by bacteria, fungi and other organisms that may produce cancer-producing metabolites. And, of course, we can introduce through the mouth an ever-increasing number of chemicals for medicinal, cosmetic and pleasurable purposes. These exposures are not limited to the technically advanced populations. The diets of primitive peoples have similar opportunities for contamination, including the addition of herbs and other "natural" products that contain alkaloids and other chemicals.

We have already alluded to the possible roles of plant and mold products in the occurrence of liver cancers among the sub-Sahara peoples. Smoked fish, charred coffee, and burnt meat contain impressive amounts of identifiable benzopyrene and have been suggested as factors in the occurrence of cancer. It should be pointed out that the actually burned portion of such produce is seldom ingested because it is unpalatable. The supposition that smoked fish is a causative factor in the high incidence of gastric cancer in Iceland was not supported by more careful field research. An equally high gastric cancer rate is found in Japan, where fish is not smoked but preserved in salt.

Cancer-producing chemicals and other agents that gain access by the oral route may produce their effects at sites distant from the gastrointestinal tract. The end-effects depend to a great extent upon the metabolic pathways and the route of excretion or disposition of such materials. When radium or radioactive strontium is ingested, the elements are deposited in bone, and bone sarcomas are induced. The azo dyes on ingestion produce the carcinogenic reaction in the liver. The fluorenes induce tumors of the breast and of the ear as well as in the liver of rats. Diethylstilbestrol and other compounds with estrogenic activity introduced by the oral route exert their carcinogenic potential in the breast and other distant target tissues, but not on the gastrointestinal tract. The polycyclic hydrocarbons on ingestion will produce intestinal cancers in mice, but also induce lung tumors, leukemia and breast cancer in susceptible strains of rats.

Volatile and particulate materials suspended in the air are not only inhaled, but usually ingested as well. The absorption of such materials is therefore not limited to the respiratory tract but also may proceed through the gastrointestional tract. Important effects may be derived from a combined action of several cancer-producing and cancer-stimulating agents through different routes of entry. For example, mice given small doses of carbon tetrachloride by mouth become more liable to develop tumors following injection of polycyclic hydrocarbons. Perhaps a combination of oral alcohol and the inhalation of smoke may represent a similar situation in man, as in the occurrence of cancer of the esophagus in people who drink and smoke to excess.

Powerfully carcinogenic nitrosamines can be formed in the stomach from nitrites and amines in the diet. The amounts are very small and the products are unstable, but the observations also raise intriguing possibilities that such processes may have a role in the induction of cancers of the gastrointestinal tract in man.

The gastrointestinal tract harbors a world of microorganisms. Many of these are saprophytic, or even useful to the host. The role of bacteria is better understood by the development of germ-free animals. The animals are removed from the uterus by sterile surgery, and live out their lives in air-tight tanks from which all bacteria are excluded. Germ-free animals develop cancer when injected with cancer-producing chemicals.

A definite role for bacteria is found in cycasin, a product of the *Cycas circinalis* palm nut that is eaten by natives of Guam and other Pacific islands. Cycasin fed to rats produces cancer of the kidney and several other tissues. Germ-free rats do not develop cancers. Intestinal bacteria have to split cycasin into an unabsorbable glycone and the cancer-producing chemical, methylazoxymethanol. The latter is absorbable, and is cancer-producing in germ-free rats as well as in conventional animals.

Animals fed nitrosamine derivatives that cause gastrointestinal cancers develop more tumors when their diet is rich in fats. Promotion of the carcinogenic effect may be due to better absorption of the chemical, or to alteration of the bacterial flora of the intestine. The work on cycasin, and on the effects of diet upon carcinogenesis, have reawakened interest in the role of gastrointestinal flora in the transport and metabolism of carcinogens and their precursors.

18. Immunity

Trained guardians against invasion

Disease represents a reaction of the organism against some harmful agent or circumstance, from external or internal sources. The balance in the reaction may favor the host, in which case the disease is overcome with or without sequelae. It may favor the causative stimulus to a degree that results in death of the organism. Or the process may achieve a constant or undulating balance between the stimulus and the host.

The reaction of the host is often referred to as "resistance." An individual catches a cold, or dies from an usually mild disease, and we will hear that his "resistance was low." This is a relatively meaningless term, because we seldom can measure resistance, or the virulence of the stimulus which confronted the individual.

One type of resistance is the ability of the body to get rid of the harmful stimulus. A portion of an organism's defense, or resistance, to carcinogenic polycyclic hydrocarbons is a well-functioning liver

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that can detoxify and eliminate these noxious chemicals from the body. Newborn rodents are more susceptible to many carcinogenic chemicals than adults, in part because the full complex of detoxifying enzymes of the liver develops following birth. Detoxifying enzymes of the organism can be overwhelmed by using larger doses of the chemical, as well as by lowering the host resistance by, for example, reducing hepatic efficiency by carbon tetrachloride.

Another type of resistance is manifested by *immunity*. Experience going back to antiquity showed that individuals who recovered from such diseases as smallpox were nearly always safe from ever catching the disease again: they were immune. Edward Jenner of England assisted nature's process by showing in 1796 that a milder form of a related disease, vaccinia of cattle, would protect against virulent smallpox. Pasteur's great contribution was the production of immunity by injection of the dead organism of anthrax. Thus, the live, attenuated or killed bodies of several types of bacteria and virus produce a reaction in the body that empowers the organism to protect itself against later onslaughts of these agents.

The immune reponse of individuals to bacterial and viral diseases is not expressed as an all-or-none reaction. Partial immunity is manifested by the development of mild or attenuated disease, or, in fact, by subclinical infections. The same effects can also be due to exposure to less virulent strains of organisms.

Paul Ehrlich during the early part of this century, and many scientists following him showed that immune reactions are due to the manufacture of specific proteins by cells. These proteins tie with and inactivate foreign proteins such as are found not only in bacteria and viruses but in plants, milk and a galaxy of other products. The impress of these foreign antigenic "keys" stimulates the cells to produce "locks" of antibodies.

Immunity involves lymphocytes, motile body cells that are found in the blood, lymph and tissues. There are two main classes of lymphocytes. The B-lymphocytes evolve in the bone marrow and make antibodies that are secreted. The T-lymphocytes arise in the thymus gland and are concerned with cellular immunity, attaching themselves to surface antigenic sites of cancer and other cells recognized as foreign.

Clinically, cancer is manifested by a great diversity in its course. Some cancers of the breast grow very rapidly and kill the individual within a few months after diagnosis, while others, seemingly identical, progress slowly; some metastasize widely while the primary tumor is still small, whereas others remain relatively localized for many years. Some tumors, especially the neuroblastomas of childhood, melanomas of the eye, and breast cancers, undergo temporary and even seemingly permanent regressions. One of the possibilities is that these tumors stimulate a form of an immune response in the patient. The study of this possibility is an attractive area for research.

Early experiences with transplanted tumors in noninbred mice and rats showed that many of such tumors grow for a short time and then disappear. The animals would then be immune to further transplants of the same tumor. High hopes were aroused that immunologic treatment of cancer could be achieved, but it was soon demonstrated that immunity to transplanted tumors was not specific against tumors and a manifestation of a foreign tissue rejection. The disappointments led to a swing toward the opposite extreme, the belief that cancers were too similar to normal tissues to produce immune responses.

George Klein, of Sweden, and Richmond Prehn, of Philadelphia, were among the workers who returned to the field of tumor immunology some 15 years ago, and established that many induced and spontaneous tumors did, indeed, contain antigens that evoked immune responses in the host. These antigens were weak, and had to be detected by more subtle methods than were applicable to bacterial diseases. The tumor-related antigens in tumors induced by oncogenic viruses retained the imprint of these viruses, so that they were virus-specific.

Antigens in "spontaneous" tumors without viral association or in tumors induced by chemical carcinogens, in contrast, varied widely and were much weaker or not demonstrable. Some antigens are hidden in the cell nucleus, or are protected at the cell surface by "blocking antibodies."

The immune response of an organism is one of its manifestations of identity. The genetic mosaic of the body and its cells recognizes and rejects nonidentity. This is the basic mechanism for the nonacceptance of skin or other tissue grafts between individuals with genetically different characteristics. Several important lines of investigations have yielded methods by which this immune basis of individuality can be depressed. This work has already allowed the opening of a new, long-dreamed-of era in surgery, of replacing organs such as kidneys.

Immune responses can be decreased by several procedures: large doses of cortisone, X-rays and certain antimetabolites that block the formation of nucleic acids. The responses can also be modified by chemical changes in the transplanted tissue, such as by preservation of blood vessels and bone. Peter B. Medawar of Great Britain and Macfarlane Burnet of Australia shared the Nobel prize of 1960 in medicine for their studies on transplantation of skin and other tissues in embryos and newborn animals. If an embryo is injected with tissue from a foreign embryo, the immune reaction is not evoked, and the animal will later accept tissue from the foreign adult recipient because it is no longer immunologically recognized. Studies of this mechanism have indicated that the immune response in rodents develops after birth.

The change of normal cells to neoplastic cells is associated with the appearance of new or different proteins that the body recognizes to be foreign. It has been postulated that perhaps most cancer cells are eliminated by an early immune reaction, a body surveillance. Robert A. Good and others have shown that immune-deficient patients develop many more cancers of the lymphoreticular type than normal people. Immune deficiency can be hereditary, or can be induced by drugs such as are used in patients who receive kidney transplants in order that the body not reject the transplant.

Immunology is also important in research on tumor viruses. Earlier work with adult birds indicated that the Rous virus was quite species-specific; that is, it would survive and produce tumors only in chickens. Now, with the use of newborn animals, and the additional methods of blocking immune response with cortisone, as well as the activation of virus by passage through tissue culture, the dogma of species specificity of tumor viruses is completely demolished. The polyomavirus exhibits wide cancer activity in several species, and even the Rous chicken virus has now been shown to induce cancers in rats and in monkeys. Although it is still in the realm of conjecture, the possibility of animal tumor viruses being able to infect human beings, while in the uterus or in the immediate period following birth, can no longer be dismissed.

Immunology is now one of the liveliest, most promising areas of contemporary cancer research. As is usual in science, much of the progress is due to development of instruments and techniques in immunochemistry and the physicochemical separation of tissue components. Molecular biologists are unraveling the chemical structure of antibodies, work that has already claimed one Nobel prize.

On the clinical level, immunotherapy is being cautiously explored as an additive form of treatment, especially in patients with immune responses suppressed by their disease or by immunosuppressant drugs. Blood or lymphocytes from patients who recover from cancer, particularly the rare individuals who undergo spontaneous regression of their cancer, are being investigated for therapeutic effects.

Attempts are also being made to increase immune responses by nonspecific stimulants, such as vaccination with BCG, attenuated bovine tuberculosis used to protect against human tuberculosis. BCG is being tried as an additional measure in the treatment of leukemia, melanoma and other forms of cancer.

A deworming drug, levamisole, also stimulates cellular immunity. Immunologic agents of interest include thymosin, an extract of the thymus gland that includes maturation of T-lymphocytes, and the interferons, antiviral substances produced by mammalian cells.

Immunization is best achieved by first identifying the causative antigen. Thus, mammary cancers in mice can be prevented by immunization against the causative Bittner virus. A lymphatic cancer in chickens, Marek's disease, is prevented by vaccines of attenuated or avirulent strains of the causative DNA virus. Vaccines against some of the human candidate viruses noted in chapter 10 are possibilities for the future.

19. Chemotherapy

A frontal attack

One scholar of cancer in 1945 expressed the opinion that to find a chemical that would make cancer disappear and leave normal tissues unharmed was almost equivalent to finding a drug given by mouth that would dissolve one ear and leave the other in place. And, up to that time, with the research literature littered by negative reports and by tarnished reputations of investigators, this pessimism was perhaps justified.

Two discoveries, however, led to a revision of scientific opinion that stimulated a renewed interest in the chemotherapy of cancer. The first was an accidental observation during World War II, that a potent war gas, nitrogen mustard, produced selective damage to the lymphatic system and the bone marrow. Under the cloak of wartime secrecy, the compound was tried cautiously in patients with cancer of these tissues, leukemia, lymphosarcoma and Hodgkin's disease. Remarkable temporary remissions of the diseases were achieved in a good proportion of such patients.

The other discovery was made through investigations that sought to block metabolic processes of cells by providing the cells with

chemical relatives of essential materials that the cells could not distinguish but which did not fulfill their needs. These are the "antimetabolites." One of the early compounds of this nature, methotrexate, was shown by Sidney Farber of Harvard to have beneficial effects in children with acute leukemia. Apparently the leukemic cells were affected to a greater extent than normal cells by the interference of metabolic reactions requiring folic acid.

These findings were used by Farber and by Cornelius Rhoads of the Sloan-Kettering Institute in New York as evidence for the need of expanded drug-development and testing programs, and received sympathetic response in our Congress. By 1955 a large national program of cancer chemotherapy was organized in the United States, and is still in full swing. Over 500,000 chemicals and other materials have been tested on laboratory animals, and several hundred chemicals were deemed sufficiently effective and interesting to be tried in patients with cancer. The British workers entered the field with great force and achievement at the same time, and there are important chemotheraphy programs in Germany, the Soviet Union and Japan. Some 40 drugs are now commercially available for the clinical treatment of cancer; may of these are named in the table on page 21.

Research in the chemotherapy of cancer can be divided into four main steps: the selection of the chemicals or other materials to be tested; the bioassay of the material on some animal tumor system; preclinical pharmacology of agents that are selected on the basis of antitumor effects in animals; and, finally, clinical trials.

The selection of agents to be tested may be made in several ways. Of course, the nearest method would be to start with a clear hypothesis, and plan for the specific chemicals by which the hypothesis can be tested. This is the "rational" approach. The extreme opposite of this is blind empiricism, in which any chemical is swept off the shelf and introduced for animal testing. In most instances, the choice is based on considerations somewhere between these two extremes.

One type of rational but secondary approach is the systematic expansion of known leads. For example, if one antifolic acid compound shows a definite effect, the chemists are asked to synthesize a wide range of chemical relatives or analogues. The principle of metabolic interference is also applied not only to vitamins, but to purines, pyrimidines and other chemicals that are known to be involved in cellular synthesis and metabolism. This approach has yielded some valuable additions, such as 6-mercaptopurine. The antimetabolite area is attractive to the research worker because it contributes to the understanding of cellular metabolic processes even if the aim of anticancer effect is not reached.

Nitrogen mustard is one of several hundred very reactive alkylating chemicals, some effects of which in tissues resemble those of ionizing radiation so that they are referred to as "X-ray mimetic." Like X-rays, these chemicals not only inhibit some forms of cancer but also can produce cancers, and also cause germinal mutations. The alkylating "war head" can be attached to amino acids, sugars, and other chemicals of metabolic importance, with the hope that these will guide the reaction to a specific target.

Organic chemists have also created hundreds of steroids and related compounds with various spectra of hormonal activity, as potentially useful agents for some forms of cancer. The discovery that L-asparaginase is active against childhood leukemia added enzymes and other proteins to the area of chemotherapeutic exploration. An organic platinum compound, *cis*-platinum diamine dichloride, is an example of a new class of agents with activity against testicular and ovarian cancers.

The choice of materials is not limited to defined chemicals. Several antibiotic products of fungi and bacteria, such as actinomycin and mitomycin, have been found to have cancer inhibiting activity. A systematic exploration of cultures of microorganisms for such effects became a natural part of the program. Crude but defined products of plants have led to the isolation of yet another group of active anticancer agents such as vinblastine and vincristine, from the periwinkle plant (*Vinca rosea*).

The second phase of the chemotherapy program involves the testing of the selected materials on animals with tumors. Here the investigators are confronted with a number of difficulties. How similar are the cancers of mice or rats and those of man? With what assurance can we predict that an agent that shows an effect on some animal with a tumor will have an effect in a patient with cancer? To answer this question, large amounts of data are necessary for analysis, and probably no single answer will ever be forthcoming. It would be really too much to ask that any one, or a few, types of cancers in animals would have the same responses as the hundred-odd different types of cancer in man. A practical approach to this problem was to select the animal tumors that on previous experience paralleled human tumor responses. Despite the known shortcomings of transplanted tumors, these are still the ones that are most uniform in their growth and other characteristics and are obtainable in sufficient numbers for the large-scale programs. With additional experience and correlations with clinical trials, less useful animal tumors are replaced in the system. Induced and spontaneous tumors in rodents are also used for agents of particular interest, as well as human cancers grown in cheek pouches of hamsters and in rats that are given cortisone to depress their immune response.

With the analysis of a large body of data, there is now good reason to base chemotherapy investigations directed against human leukemia on several transplanted leukemias in mice, such as the L1210 tumor. Better experimental models for more limited types of human cancers are being found and will allow more rapid and more confident choices of materials for actual human trial.

The third step in the investigational process is preclinical pharmacology. Agents that affect animal cancers adversely or prolong the life of the animals, or show other beneficial effects, have to be tested further for safety and for determination of routes of administration, dose levels, schedules, and the vehicles for use in man. Acute toxicity is usually determined first in rats, and is extended to acute and chronic toxicity studies in rats and dogs, with other species including monkeys as considered indicated. Very important are the investigations of the metabolic pathways and mode of action of the chemicals. These studies are greatlv facilitated by radioactive-isotope tagged chemicals, making it easier to detect the absorption, deposition, excretion and reactions of the agent within the body. Even the most extensive research preparation on animals, however, does not completely eliminate hazard, untoward reactions and other risks when the agent is finally selected for exploration in man. Of course, when we deal with a fatal disease such as advanced cancer, somewhat earlier clinical trial is justified than would be, for example, for the common cold. Nevertheless, in the last analysis the decision to perform a clinical trial rests on the consideration of all available data on the chemistry, action, toxicology and pharmacology by a technically competent group of investigators from the clinical and biological sciences.

Clinical trials in cancer proceed through three phases. The first is the cautious administration to patients of a fraction of a dose of material that has been found to be safe in rats, dogs and other animals. The dose is then gradually increased, and all appropriate observations for toxic or beneficial reactions are recorded and analyzed. At this point the drugs are tried in patients with very advanced cancer who have exhausted the possibilities of all standard and useful medical measures. Their participation in the trials is voluntary and with their full consent. The chief aim is to assure that further trial of the agent is indicated and safe.

Phase two of the clinical trials consists of a more intensive search for anticancer effects in patients with as many types of cancer as possible, unless the agent is designed for, or for other reasons may be predicted as having effects in a limited variety of cancer entities. From a practical standpoint, this phase involves a collaboration among clinical centers, in order to obtain results during a reasonable time. The more common human cancer entities such as cancers of the lung, large intestine, breast and leukemia, are chosen for the same reason. Again, only patients beyond possible cure or benefit by known procedures are accepted, and the patients are informed and they agree to participate in the studies. Most suitable are patients with measurable, visible lesions, allowing frequent quantitative observations on the course of the disease. This phase establishes whether the agent is ineffective or does have sufficient objective effects on cancer to justify further clinical use.

Phase three of the clinical trials is usually limited to drugs or procedures that have been established as having a beneficial effect. They attempt to quantitate the response, and to compare it with another drug or procedure. A typical question such trials answer is whether nitrogen mustard or a newer alkylating agent, at specific dose schedules, is superior for the management of a particular type of cancer, such as Hodgkin's disease. In cancers for which no recognized beneficial treatment is available, the control group may receive an inert "placebo." The best design for these studies is one in which neither the patient nor the physician knows whether the patient is getting one or another drug. This is known as a "double-blind" method. The inclusion of patients is still on a voluntary basis, but the whole purpose of the study would be defeated if the nature of the treatment were known by the individual patient. Thus, patients enter one or another of the groups to be compared by laws of chance, through a procedure called "randomization," which allows for an equal distribution of known and unknown differences between patients and avoids selection.

The search for chemicals against cancer has broadened to the simultaneous use of several chemicals that affect different phases of cell division or different metabolic pathways. Additions of immunotherapy to chemotherapy, or the simultaneous use of radiation, chemotherapy and immunotherapy are also being tried clinically as well as in animals. The experimental design for such combinations becomes increasingly complex.

As indicated in chapter 4, chemotherapy is now part of many standard treatments against cancer. Curative effects are obtained against some cancers characterized by rapid cellular proliferation. Truly effective drugs for the more frequent cancers, such as cancers of the lung, breast, colorectum, and prostate, remain still in the future.

But greater victories over cancer do not have to await discoveries of more effective cures. Knowledge of one's body and prompt medical attention to signs and symptoms that may connote cancer (as described in chapter 3), should improve the outlook following treatment methods already available.

A significant decrease in cancer can be achieved also by prevention. Reduction of chemical and physical carcinogens in our environment (chapters 7 and 8) would reduce the cancer burden. Avoidance of tobacco smoking (chapter 9) is probably the single most important individual method by which cancers of the lung and several other sites can be prevented. Dietary habits that avoid excessive calories and fats, and contain all essential nutrients, should be rewarding in controlling heart disease as well as cancer.

Prevention depends upon individual commitment, medical assistance, and public policy. All are dependent upon knowledge.

20. The past and the future

Victory is a reasonable expectation

Scientists do not relish being cast in the role of soothsayers, yet prediction is one of the important functions of science. The research method yields the necessary knowledge that makes predictions more reliable, and allows man to some extent even to modify the course of future events.

So it is in cancer research, which started at the turn of this century. Its broad aims were well defined from the beginning: to find knowledge that will allow us to prevent and to cure cancer. The approaches to these goals are through the study of causative factors in the initiation of cancer, and of the nature of the cancer process, including its effects on the host.

We have come a long way since the founding of the Imperial Cancer Research laboratories in England in 1903, the creation of the National Cancer Institute in the United States in 1937, and the expansion of the American Cancer Society in 1944. The National Can-

cer Act of 1971 reaffirmed the desire and confidence of the public by a concrete political act backing the optimism of scientists. Cancer research programs in Europe and in Japan indicate a worldwide involvement in this biomedical adventure against the most dreaded of diseases.

What has been learned during three-quarters of a century of research? The question is not only of historical interest but has contemporary relevance. For, as Byron wrote, the best prophet of the future is the past.

The first half of the history can be divided into two major periods, essentially by the materials available for experimentation. The first was the transplantable tumors of rodents, which provided knowledge regarding the biology and morphology of experimental tumors. During the same period, mammalian geneticists provided genetically defined animals and explored the hereditary factors in cancer. The second period dealt with induced tumors, primarily those elicited by tar.

The modern period of cancer research can be dated from the 1930's, when chemical carcinogens and steroid hormones were isolated. Although the first carcinogens were of environmental origin, research turned to studies of body metabolism following the synthesis of one related compound from bile.

Following World War II, during which the anticancer activity of nitrogen mustard and of antifolates was discovered, the predominant wager was placed on chemotherapy. Important systemic treatments were uncovered for rapidly proliferating cancers.

The scientific investment during the 1960's favored viruses. A decade of intense effort added knowledge to cell-virus interactions, and the role of latent viruses that lurk in the genetic mechanisms of mammalian cells. Although no human cancer has been proved to be of viral origin by 1978, despite dozens of examples among animals, we may be at the threshold of such a demonstration for man.

During the 1960's the dogma that cancer did not arouse an immune response from the host was overthrown. Cellular immunity has led to the identification of proteins that arouse lymphocytes to manufacture antibodies, and the interaction at cell surfaces. Greater specificity of antigens may yield important therapeutic as well as preventive results.

During the 1970's we are also back to environmental carcinogens, in our surroundings, our diet, and our way of life. Epidemiology developed to full stature, allowing research on populations. There is a consensus that a significant proportion of cancers are elicited by environmental agents and situations, the elimination of which may well reduce the cancer burden. The important role of social and behavioral aspects is evident in the lack of abatement of the tobacco smoking habit despite proof that it is an important cause of cancer.

Biomedical science is delving ever deeper into the very interstices of living matter. Molecular biology has already learned how to manipulate the DNA molecule, recombine it, and introduce it into another species. In this new arena, cancer research is an important contributor. Cancer is a cellular attempt to cast off the biological limitations of death and renewal, and to acquire a specious parasitic immortality. It is a caricature of normal cellular behavior, and illuminates many aspects of normal biology as well as its deviations.

The extent and the cost of cancer makes it a public, social problem as well as a problem for biomedical science. Activities against cancer do not stop at the doors of laboratories or hospitals, but reach into the community. As monetary allocations against cancer rise to become visible in national budgets, and as the activities increasingly involve all of the health care system, considerations of cost-benefit ratios become ever more compelling.

The cost-benefit ratio underlies many individual as well as social decisions. A drug prescribed against an illness must be weighed as to untoward reactions. The greater the potential benefit and the greater the danger, the greater can be the acceptable risk. A life-threatening situation requires measures other than those suitable against an annoyance.

Cost-benefit ratios become more complicated when they involve groups of people. What risk, and resultant cost, should be accepted in the use of sex steroid replacement for menopausal symptoms? What balance weighs relief of symptoms against a small but real increase in uterine cancer?

One calculation of cost-benefit ratio that is unacceptable is when the costs are borne by one group and the benefits by another. This can occur when industry takes risks with the health of workers, or when tobacco interests advertise their products as safe and desirable.

In the social dimensions of cancer, feedback of research findings to the public is essential if the activity is to maintain public support. The American public is too sophisticated to expect instant miracles, but it does expect to be informed and be included in the benefits for which it has paid. Thus, the National Cancer Act mandates the creation of regionalized cancer centers, public and professional education programs, and other methods by which information and benefits can be transmitted to the public.

The generous public support of anticancer activities gives rise to a series of questions in which cost-benefit considerations are involved. What proportion of the national budget for biomedical research should be ear-marked for cancer? What is the correct balance between cancer treatment facilities and more general health care centers? Are the expenditures commensurate with the benefits, and how are the benefits to be measured?

There are no simple answers to these and a myriad of related questions. At best, the aim should be to find reasonable balances modifiable by new circumstances. Were there an anticancer cure-all discovered tomorrow, much of what is serious and vexing would become trivial. Thus, even in the societal dimensions of cancer, research is the key for the resolution of our problems.

Whether now or later, however, certain principles retain their verity. One is that an informed, motivated population is the basic requirement for correct decisions in health as well as other societal actions. Public information should be accurate and not diluted by propaganda from vested interests and anti-intellectual sources. Education must start early in life, preferably through antecedent generations, and continue for life.

The guiding principles of action against cancer and other chronic diseases of our time are *life-style* and *body awareness*. Our individual decisions of what and how much to eat, how to live, and whether to smoke or to drink will have more influence on our health than therapeutic medicine directed at repairing the damage of our indiscretions. Individual habits must be coupled with knowledge of when to seek medical counsel, either for surveillance of our bodies or attention to signals of distress. This medical role cannot be delegated safely to well-meaning friends or subprofessionals.

The exercise of desirable health habits and conduct must go hand in hand with a healthy environment and safe products distributed to the public. This requires group political action, effective regulatory measures, and constant monitoring and involvement. All of which raises more problems of cost-benefit ratios.

Many citizens of the United States feel that they are already over-regulated and overtaxed, and their voices are rising in number and in intensity. How far should the political-police arms of society impringe upon individual rights, even when such rights are deemed to be foolish or harmful? Should the sale of cigarettes be prohibited? Should treatment of mentally incompetent individuals with hopeless cancer be mandated by the courts?

As for prophesies, it should be sufficient to repeat the words written in 1927 by H.G. Wells: "The disease of cancer will be banished from life by calm, unhurrying, persistent men and women, working with every shiver of feeling controlled and suppressed, in hospitals and laboratories, and the motive that will conquer cancer will not be pity nor horror; it will be curiosity to know how and why."

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Glossary

ABERRANT: Deviating or wandering from the normal or usual course.

ACROMEGALY: Increase in size of short and flat bones, especially of hands, feet, and face, without an increase in height.

AFLATOXIN: Cancer-producing chemical made by a mold, *Aspergillus flavus*.

ALIMENTATION: The act of giving or receiving nutriments.

ALKALOID: Naturally occurring, basic, organic nitrogenous compound, usually of plant origin.

AMINO ACID: One of the chief chemical compounds of which proteins are made.

ANDROGEN: Male sex hormone.

ANTIBIOTIC: An antibacterial substance produced by a living organism, such as a fungus.

ANTIBODY: Specific substances produced by the body as a reaction to antigen and which react with the antigen.

ANTICARCINOGEN: An environmental agent offering some protection against a carcinogen.

ANTIGEN: A substance that incites the formation of antibodies or an immune response.

ANTIMETABOLITE: A closely similar but inactive compound which tends to replace an essential cell building material.

ASEPSIS: Absence of septic matter, or freedom from infection.

BCG: Abbreviation of Bacillus Calmette-Guérin, an attenuated bovine tuberculosis germ strain used in vaccination against tuberculosis.

BENIGN: Not malignant; not recurrent.

BENZOPYRENE: A hydrocarbon constituent of coal tar.

BIOPSY: The removal and microscopic examination of tissue from the living body for purposes of diagnosis.

BURKITT'S LYMPHOMA: A lymphatic cancer of the jaw in children of sub-Sahara Africa.

CARCINOGEN: A chemical or other environmental agent that produces cancer.

CARCINOMA: A malignant tumor or cancer made up of epithelial cells.

CHEMOTHERAPY: The treatment of disease by chemicals which act as drugs in the body, without producing serious toxic effects on the patient.

CHIMERA: A plant or other organism exhibiting two genetically distinct types.

CHROMOSOME: One of several small, more or less rod-shaped bodies in the nucleus of a cell. The chromosomes contain the hereditary factors (genes) and are constant in number in each species.

COCARCINOGEN: An environmental agent which acts with another to cause cancer.

COLOSTOMY: The operation of forming an artificial opening into the colon.

CORTISONE: A steriod hormone produced by the adrenal glands.

CYCASIN: Cancer-producing chemical in a tropical palm nut.

CYTOPLASM: The protoplasm of a cell exclusive of the nucleus.

DEDIFFERENTIATION: Reversal of differentiation of a tissue, to a more primitive, embryonic stage.

DEOXYCHOLIC ACID: One of the unconjugated bile acids.

DIFFERENTIATION: The process of acquiring distinctive characteristics, such as occurs in cells and tissues of the embryo.

DNA (deoxyribonucleic acid): One of the two kinds of nucleic acids found in all cells. The other is RNA (ribonucleic acid). These exert primary control over life processes in all organisms.

DIETHYLSTILBESTROL: Synthetic compound with estrogenic activity.

ELECTRON MICROSCOPE: An optical instrument using a beam of electrons to produce a magnified image on a fluorescent screen or photographic plate.

ENDOGENOUS: Originating or developing within the organism.

ENZYMES: Complex organic compounds (proteins) produced within an organism, capable of accelerating a particular chemical reaction; a catalyst.

EPIDEMIOLOGY: Medical science concerned with the occurrence and distribution of disease in human populations.

EPIGENETIC: Not involving the genetic mechanism of the cell, especially DNA of the nucleus.

ESTROGEN: A female sex hormone.

ESTROGEN RECEPTOR: Site on cells at which estrogen molecules attach and penetrate to produce estrogenic effect.

ETIOLOGY: The science or study of the causation of any disease.

EXOGENOUS: Originating or developing outside an organism.

GENE: A segment of a chromosome which contains a unit of genetic information; controls a trait or process.

GLYCOPROTEIN: A chemical conjugation of carbohydrate and protein, found especially in cell membranes.

HERPESVIRUS: The DNA-type virus that causes herpes diseases, usually blisters of the skin, genitals, and mouth.

HODGKIN'S DISEASE: A form of cancer affecting the lymphatic and other tissues which play a part in the individual's ability to fight infection.

HOMEOSTASIS: A tendency to uniformity and stability in the normal organism.

HORMONE: Chemical substance produced in one part of a plant or animal body that is transported in the body fluids to another part of the body where it exerts a specific effect.

IMMUNITY: The power which a living organism possesses to resist and overcome infection.

INTERFERON: Special proteins made by cells to fight virus infection.

IONIZING RADIATION: Radiation which separates molecules into charged particles (ions). Causes physical and genetic damage to the human body.

LACTONE: A reactive organic compound of the type known as cyclic esters; some lactones are carcinogenic.

LASER: (*L*ight *A*mphification by *S*timulated *E*mission of *R*adiation.) An optical instrument that emits an intense beam of monochromatic, coherent light.

LEUKEMIA: Cancer of the blood-forming tissues, characterized by a marked increase in the number of leukocytes (white blood cells) in the blood.

LYMPH: An almost colorless liquid composed of tissue, fluid and proteins, found in the lymphatic vessels of the body.

LYMPHOSARCOMA: A cancer arising in lymphatic tissue.

MALIGNANT: Tending or threatening to produce death.

MASTECTOMY: Surgical excision of the breast.

MEDICOLEGAL: Pertaining to medicine and law.

MELANOMA: A skin tumor containing dark pigment (melanin).

METASTASIS: The transfer of disease from one part of the body to another. In cancer the new growths are like the original tumor.

MITOCHONDRIA: Rod-like structures in cytoplasm of cells, involved in respiration and energy functions.

MUTATION: In biology, a permanent transmissible change in the characters of an offspring from those of its parents; also an individual showing such a change.

NEOPLASM: Any abnormal formation or growth, usually a malignant tumor.

NUCLEUS: A specialized portion of the protoplasm of most cells; coordinates cellular activity.

PAPILLOMA: Tumors, such as warts, occurring in the skin or the lining of internal organs.

"PAP SMEAR": A technique developed chiefly by the late Dr.

George N. Papanicolaou for detection of cancer through the microscopic examination of cells collected from the vagina or other body cavities.

PHARMACOLOGY: The science of drugs.

PLACEBO: An inactive medicine given to satisfy the patient, or, as in experiments, to guard against psychological effects of non-medication.

POLYP: A mass of swollen mucous membrane projecting into the nasal or another cavity of the body.

PROGENY: Offspring; descendants.

RADIUM: An intensely radioactive metallic element found in minute quantities in pitchblende and other uranium minerals. The radioactivity of radium is the result of disintegration of the atom.

RIBOSOME: Large granule of RNA found in the cytoplasm of a cell; the site of protein synthesis.

RNA (ribonucleic acid): One of the two kinds of nucleic acids found in cells. The other is DNA (deoxyribonucleic acid). Seemingly concerned with the transmission of genetic information and the synthesis of proteins.

SARCOMA: A malignant tumor arising from connective tissue.

SUBCUTANEOUS: Beneath the skin.

SYNDROME: A set of symptoms and signs occurring together.

THYMUS: A ductless gland situated in the anterior upper chest cavity.

TISSUE CULTURE: The technique of growing plant or animal cells in test tubes outside the body but using a medium containing a variety of nutrients.

TOMOGRAPH: An X-ray picture of a layer of tissue at any depth.

TUMOR: An abnormal mass of tissue.

ULTRAVIOLET RAYS: Invisible rays beyond the violet end of the visible light spectrum. The rays have short wave lengths.

X-RAYS: Any radiations of same nature as light, but of an extremely short wavelength. Can penetrate various thicknesses of solids and form an image on photographic film.

best copy available

Throughout his career Dr. Michael B. Shimkin has participated in press conferences, science writers' seminars, television and radio programs, and has written articles to help interpret cancer research to the public. He received his medical degree from the University of California in 1937, joined the U.S. Public Health Service as a research fellow in 1938, and retired from the service with the rank of Medical Director in 1963. He was Professor of Medicine at Temple University School of Medicine, in Philadelphia, for 6 years and is now Professor of Community Medicine and Oncology at the University of California at San Diego.

Dr. Shimkin has conducted and directed extensive programs of laboratory, clinical and epidemiological research on cancer. He has made several official tours of research institutions in the Soviet Union and served as adviser to United Nations and World Health Organization programs. He was Scientific Editor of the *Journal of the National Cancer Institute*, 1955-1960 and Editor of *Cancer Research*, 1964-1969. He was Chairman of the American Cancer Society's Committee on Lung Cancer and Committee on Breast Cancer. In 1973, he was President of the American Association for Cancer Research. He continues as a consultant to the National Cancer Institute. Dr. Shimkin has published 300 professional papers on clinical and laboratory cancer research, and a history of cancer, entitled "Contrary to Nature."

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"Science and Cancer" is addressed primarily to the informed reader outside the scientific community. This book will be most useful to those who have had a high school course in biology, for it assumes a familiarity, on the part of the reader, with the life processes in which neoplastic disease seems to be thoroughly involved. It describes the nature of cancer, its effect on the organism in which it resides, and the efforts of scientists and physicians to learn more about it and thus to deal with it more effectively. Although the entire field of cancer research is examined, "Science and Cancer" draws its focus mainly on the disease in man.

NCI
National Cancer Institute

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